Trends in oral drug bioavailability following bariatric surgery: examining the variable extent of impact on exposure of different drug classes

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Changes to oral drug bioavailability have been observed post bariatric surgery. However, the magnitude and the direction of changes have not been assessed systematically to provide insights into the parameters governing the observed trends. Understanding these can help with dose adjustments.

WHAT THIS STUDY ADDS

- Analysis of drug characteristics based on a biopharmaceutical classification system is not adequate to explain observed trends in altered oral drug bioavailability following bariatric surgery, although the findings suggest solubility to play an important role.

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AIMS

To identify the most commonly prescribed drugs in a bariatric surgery population and to assess existing evidence regarding trends in oral drug bioavailability post bariatric surgery.

METHODS

A retrospective audit was undertaken to document commonly prescribed drugs amongst patients undergoing bariatric surgery in an NHS hospital in the UK and to assess practice for drug administration following bariatric surgery. The available literature was examined for trends relating to drug permeability and solubility with regards to the Biopharmaceutics Classification System (BCS) and main route of elimination.

RESULTS

No significant difference in the 'post/pre surgery oral drug exposure ratio' (ppR) was apparent between BCS class I to IV drugs, with regards to dose number (Do) or main route of elimination. Drugs classified as 'solubility limited' displayed an overall reduction as compared with 'freely soluble' compounds, as well as an unaltered and increased ppR.

CONCLUSION

Clinical studies establishing guidelines for commonly prescribed drugs, and the monitoring of drugs exhibiting a narrow therapeutic window or without a readily assessed clinical endpoint, are warranted. Using mechanistically based pharmacokinetic modelling for simulating the multivariate nature of changes in drug exposure may serve as a useful tool in the further understanding of postoperative trends in oral drug exposure and in developing practical clinical guidance.

Introduction

Obesity is generally defined by the body mass index (BMI = body weight (kg)/height (m)²). The classification is somewhat arbitrary such that 'overweight' means a BMI ≥ 25 but <30 kg m⁻², 'obesity' refers to BMI ≥ 30 but <40 kg m⁻² and 'morbid obesity' is a BMI ≥ 40 kg m⁻² (this may also refer to being obese and suffering from related co-morbid conditions) [1, 2]. Over the last decade the prevalence of obesity has increased dramatically in the USA and Europe. In the USA 32.2% of the male and 35.5% of the female population over the age of 20 years were characterized as obese in 2007–2008 [3]. The United Kingdom has the highest reported obesity rate in Europe [4]. In England, 24.1% of the male and 24.9% of the female population over the age of 16 years were classified as obese in 2008 [5]. Bariatric surgery has proven to be successful in treating morbid obesity. In the USA and Canada approximately 200 000 bariatric surgeries were performed in 2008 [6]. In England 4221 surgeries were performed in 2008/09, an increase of over 100% since 2006/07 [1, 7]. Several bariatric surgical methods currently coexist in healthcare. These include the adjustable gastric band (AGBD), sleeve gastrectomy (SG), biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD-DS) and Roux-en-Y gastric bypass (RYGB) [8]. Other procedures, such as jejunoileal bypass (JIB), have been gradually phased out due to a higher likelihood of adverse events [9–11].

Bariatric surgical procedures have been well described in the literature [11, 12], where they are generally characterized as being restrictive, in terms of physiologically reducing dietary intake, malabsorptive, through reducing the ability of the gastrointestinal (GI) tract to absorb nutrients or a combination of both.

Restrictive procedures such as AGBD and SG result in a reduced gastric capacity to 15–20 ml and 60–80 ml respectively [12, 13]. The JIB, considered a malabsorptive procedure, results in a 90–95% bypass of the small intestine, retaining the duodenum, proximal jejunum and terminal ileum [9–11]. The BPD-DS, primarily a malabsorptive procedure, results in a reduced gastric volume (100–175 ml) and bypass of larger parts of the small intestine, forming a biliopancreatic canal transporting the bile juices to the distal ileum [14, 15]. The RYGB, combining restriction and malabsorption, results in the restriction of the stomach to 15–30 ml and bypass of the proximal small intestine [15–17].

Bariatric surgery imposes a number of physiological alterations known to affect the bioavailability of orally administered drugs (F_{oral}), dependent on the fraction of drug that is absorbed in the intestinal gut wall (f_a), the fraction that escapes gut wall metabolism (f_g), and the fraction that escapes hepatic metabolism (f_h) (Equation 1).

$$F_{\text{oral}} = f_a \cdot f_g \cdot f_h \quad (1)$$

f_a and f_g are highly influenced by drug specific properties, such as permeability and solubility, and the GI physiology such as gastric emptying time, GI pH profiles, small intestinal transit time, GI drug metabolizing enzymes and GI efflux transporters [18, 19]. Gastric emptying time can serve as the rate limiting step for highly permeable and highly soluble drugs as the absorption from the stomach is low [20]. The gastrointestinal pH may affect drug dissolution of permeability-limited drugs displaying a pKa within the range of the GI pH fluctuations. Small intestinal transit time can influence the drug absorption of poorly soluble or extended release drug formulations [18].

Metabolism in the gut acts to regulate oral bioavailability of drugs and other xenobiotics, and is an important determinant in the metabolism of substrate drugs [21]. CYP3A4 is the most abundant drug metabolizing enzyme in the GI tract, preceding CYP2C9/19 amongst others in order of appearance [22–25]. CYP3A4 and CYP3A5 are both present along the GI tract, where CYP3A4 expression rises towards the jejunum to decrease towards the ileum [21, 26]. GI transporters may influence the absorption of orally administered drugs and potentially also the extent of metabolism in the gut through active substrate efflux [27]. Numerous transporters are present in the gut, where P-glycoprotein (P-gp) is perhaps the most extensively studied of the GI transporters. The relative expression pattern of P-gp in the small intestine increases from the proximal to the distal parts of the small intestine [28].

The Biopharmaceutics Classification System (BCS) classifies drugs in accordance with their solubility and permeability. Solubility takes on the form of a dose number (Do), given by dividing highest dose strength in mg (M_o) by a volume of 250 ml (V_o) divided by the aqueous solubility of the drug (mg ml⁻¹) over a pH range of 1.0–7.5 at 37°C (C_s) [29]. Defining $Do \leq 1$ as highly soluble and an $f_a \geq 90\%$ as a highly permeable drug, drugs are classified as Class I (high solubility-high permeability), class II (poor solubility-high permeability), class III (high solubility-poor permeability) and class IV (poor solubility-poor permeability) [30].

The aims of this study were to identify the most commonly prescribed drugs in a bariatric surgery population and to assess existing evidence with respect to altered oral drug bioavailability post bariatric surgery. This would be carried out through methodologically reviewing the current literature, evaluating drug specific pharmacokinetic characteristics relating to solubility, permeability and main route of elimination.

Methods

Evaluation of drug utilization following gastric bypass

A retrospective audit of drug utilization by bariatric surgery patients was performed at Salford Royal NHS

Foundation Trust, Salford, UK. Data collection was performed using the hospitals electronic patient record (EPR) system, iSOFT clinical manager 1.4, which incorporates the medication prescription and administration records. A search of the EPR system was carried out for all patients under the care of a consultant bariatric surgeon. The search consisted of patients who had undergone surgery in the previous 5 months, from the 21 March 2011. The medical history of patients was initially searched to identify those having undergone laparoscopic RYGB. Patients who had a colostomy, gastric banding and reversal of gastric banding were excluded.

Data extraction was performed utilising an anonymous data collection form, maintaining patient confidentiality. Information extracted consisted of type of bariatric surgical procedure, pre surgery prescribed drug therapy and associated co-morbidities, post surgery medication including formulation changes and documented reasons behind alterations. Pre surgery medications were compared with the patients' medical charts on discharge, generally 2–3 days post surgery. Statistical analysis of trends in prescribed drugs observed during the retrospective audit was conducted using McNemar's non-parametric test ($P \leq 0.05$) in R v 2.12 (the R Foundation for Statistical Computing).

Review and analysis of oral drug bioavailability following gastric bypass

Embase (1980–2010) and PubMed (1977–2010) were searched using the following combinations of keywords: 'oral administration or bioavailability', 'absorption', 'bioavailability', 'gastric bypass', 'jejunoileal bypass', 'bariatric surgery'. In addition, references of related articles were systematically investigated for relevant publications.

Initial screening of titles and abstracts was carried out to identify those compliant with pre specified criteria of reporting observational trends in bioavailability/oral drug exposure of pharmaceutical agents following bariatric surgery or the identification of adverse events related to oral drug exposure following surgery. Studies excluded consisted of gastric surgical procedures not related to obesity, reports on nutrients or supplementation post bariatric surgery and publications written in a language other than English. Screening was carried out to determine inclusion or exclusion criteria. Information extracted included study characteristics (surgical procedure, study design, number of participants, year of publication, country of origin and time since procedure) and study population characteristics (gender, average age, average body mass index (BMI) and co-morbidities). The principle measurement of bioavailability in the analysis was area under the curve (AUC), bioavailability and steady-state plasma or serum concentration.

Observed trends in oral drug exposure were assumed to follow a log normal distribution. Quantitative analysis was carried out through estimating the mean effect size of

response ratios and their variance following a random-effect model. Statistical analysis was carried out with a two-tailed *t*-test of the standard normal cumulative distribution [31]. Statistical analysis between subgroups were carried out utilizing Welch's *t*-test ($P \leq 0.05$) of log-transformed weighted means and SDs with *post hoc* Dunn-Šidák correction ($P \leq 0.05$) using Microsoft® Excel 2003 and Matlab 2010 (the Mathworks Inc).

Results

Evaluation of clinical drug utilization following gastric bypass

The search of iSOFT identified 63 patients under the care of the bariatric surgeon and 38 patients (26 female) with a mean age of 45 (range 23–64) years were eligible for data extraction after fulfilling the pre-specified criteria. The surgical procedures performed included laparoscopic RYGB ($n = 34$), laparoscopic RYGB with abdominal wall hernia repair ($n = 3$) and conversion of AGBD to RYGB ($n = 1$). Commonly treated comorbidities amongst the study population included hypertension ($n = 12$), type 2 diabetes ($n = 15$), depression/anxiety ($n = 11$), hypothyroidism ($n = 5$), osteoarthritis ($n = 11$), hypercholesterolaemia ($n = 10$) and asthma ($n = 9$).

The most commonly prescribed drugs prior to surgery included statins ($n = 13$), ACE inhibitors ($n = 10$), proton pump inhibitors (PPIs)/histamine H₂-receptor antagonists ($n = 10$) and metformin ($n = 10$). Comparing pre to post surgery, a significant increase in the prescription of paracetamol, opioids, PPIs/histamine H₂-receptor antagonists, heparin and antimicrobials was observed ($P < 0.05$) as well as an overall reduction in the number of patients treated for type 2 diabetes ($P < 0.05$). The most common drugs prescribed following surgery included heparin ($n = 38$), PPIs/histamine H₂-receptor antagonists ($n = 38$) and paracetamol ($n = 34$). The number of patients prescribed cardiovascular agents remained constant postoperatively, whereas prescriptions of statins displayed a non-significant reduction of 31% ($P > 0.05$). The postoperative formulation of choice for diuretics was liquid ($n = 4$), whereas the remaining cardiovascular agents were tablets that were being crushed postoperatively ($n = 28$) (Figure 1).

All patients receiving antidepressants remained on the same antidepressant post surgery, with all but one receiving a different formulation. Of the 11 patients prescribed antidepressants, 50% were switched on to liquid formulations, whereas the remaining 50% were advised to crush their tablets post surgery (Figure 1). All patients with a prior diagnosis of diabetes underwent a diabetic review during their stay in hospital. The review resulted in a significant reduction in post-surgical prescriptions of anti-diabetic medications by 67% ($P < 0.05$). Patients who no longer required diabetic medication were alternatively switched to manual monitoring of blood glucose concen-

Figure 1

Pharmacotherapeutic alterations in formulation properties (Solid = solid tablets, Liquid = liquid formulation, S/C = subcutaneous, Crushed = patients instructed to crush tablets, Inhaled = inhalation formulation) post bariatric surgery of prescribed cardiovascular drugs, antidepressants and antidiabetics as compared with prior to surgery observed in 38 evaluated patients. Solid (■); Liquid (■); Crushed (■); S/C (■); Inhaled (□)

trations. Metformin was the only agent continued postoperatively and in 60% of cases continued at a reduced dose of up to a third of the pre-surgical dose level. All but one patient were converted to liquid preparations (Figure 1). Standard postoperative treatment consisted of 1–2 weeks low molecular weight heparin injection, PPIs (lansoprazole FasTab) and liquid formulation pain-killers (codeine and paracetamol) being prescribed for all patients. This patient group also displayed a significant increase in the prescription of PPIs/histamine H₂ receptor antagonists, opioids, paracetamol and heparin ($P < 0.05$). One patient with a history of deep vein thrombosis remained on tinzaparin for 4 weeks.

Lansoprazole was given at a dose of 30 mg twice daily as a orodispersible formulation. The prophylactic therapy was to continue for at least 6 months postoperatively, before reducing the dose to once daily for a further 18 months. Approximately 2 weeks after surgery the sublingual formulation was switched to the solid tablet or capsule formulation.

Antimicrobials were given to seven patients postoperatively for the eradication of *Helicobacter pylori* ($n = 5$) that was detected from an intra-operative gastric mucosal biopsy, development of hospital-acquired pneumonia ($n = 1$) and anastomotic leakage ($n = 1$). All patients were given liquid preparations.

In total 17 patients were taking analgesics on a regular basis prior to surgery, increasing to 38 patients postoperatively. Analgesic products included paracetamol ($n = 2$, $P < 0.05$), aspirin ($n = 5$), opioids ($n = 9$, $P < 0.05$) and non-steroidal anti-inflammatory drugs (NSAIDs) ($n = 3$). Patients taking NSAIDs prior to surgery ($n = 3$) were advised to stop taking these postoperatively due to an increased risk of developing gastro-jejunal anastomotic ulceration.

As stated in the patients 'plan' for postoperative care, a review of the nutritional progress usually occurred approximately 2 weeks post surgery. Patients were therefore advised to cease taking any non-essential vitamins and minerals immediately after surgery until the nutritional review has been completed. On discharge patients were informed that they would require taking lifelong dietary supplementation.

Oral drug bioavailability following bariatric surgery

The initial search of Embase and PubMed identified 311 potentially relevant publications based on search terms. After screening of abstracts, 66 articles were identified of which 22 matched the pre-specified criteria following full text screening. Overall, the literature search included 41 articles (20 controlled trials, 18 case reports and three case series) published between 1974 and 2011 that were suitable for further evaluation and data extraction.

Articles relating to JIB mainly appeared between 1974 and 1985. An increase of published data on RYGB was identified between 2000 and 2011, following the trend of RYGB being the most widely used bariatric surgical procedure at the present time [1].

Surgical techniques identified included RYGB ($n = 14$), JIB ($n = 19$), reversal of jejunoileal bypass (JIB R) ($n = 4$), BPD-DS ($n = 2$) BPD ($n = 3$), GBP ($n = 1$) and AGB ($n = 1$) (Table 1). The 41 identified publications originated from the USA (58%), followed by the UK (10%), Italy (5%), Norway (5%) and Canada (5%).

A total of 230 participants were studied in the identified publications. The time point for post surgical examination of oral drug exposure ranged from 0.1 to 88.9 months [32, 33]. In total 38 drugs were identified. These were categorically divided based on therapeutic indication. The studied drugs consisted of antimicrobials ($n = 12$ drugs), cardiovascular drugs ($n = 2$), immunosuppressants ($n = 4$), antiepileptics ($n = 3$), analgesics ($n = 2$), oral contraceptives ($n = 4$), anti-ulcer drugs ($n = 1$), statins ($n = 1$), thyroid hormones ($n = 1$), antidepressants ($n = 2$), anti-cancer drugs ($n = 2$), anti-diabetics ($n = 1$) and HIV medication ($n = 1$). Postoperative trends in drug bioavailability based on

Table 1

Controlled trials examining the trend in oral drug exposure following bariatric surgery.

	Drug	Surgery	Pre to post surgery oral drug exposure ratio (X, 95% CI)	Patients (n)	References
▲	Phenoxymethyl penicillin 1000 mg	JIB	10.43 (0.10, 1058)*	3	[34]
	Atorvastatin acid 20–80 mg	BPD-DS	1.85 (0.81, 4.27)†	10	[36]
—	Ranitidine 300 mg	BPD	1.43 (1.12, 1.81)*	11	[40]
	Metformin 1000 mg	RYGB	1.20 (0.91, 1.58)†	16	[55]
	Propylthiouracil 400 mg	JIB	1.09 (0.84, 1.42)†	6	[90]
	Phenazone 15 mg kg ⁻¹	JIB	1.06 (0.81, 1.38)‡	17	[91]
	Atorvastatin acid 20–80 mg	RYGB	1.00 (0.29, 3.46)†	12	[37]
	Paracetamol 1500 mg	JIB	1.00 (0.647, 1.54)*	3	[34]
	Digoxin 0.5 mg daily (First day: 1 mg)	JIB	0.89 (0.70, 1.14)†	7	[39]
	Erythromycin 250 mg	GBP	0.61 (0.38, 0.99)†	7	[92]
▼	Sulfisoxazole 1000 mg	JIB	0.84 (0.74, 0.94)*	3	[93]
	Norethisterone 3 mg	JIB	0.80 (0.39, 1.63)‡	6	[94]
	Digoxin 0.5 mg	JIB	0.76 (0.59, 0.97)†	9	[38]
	MMF 2-1000 mg	RYGB	0.66 (0.21, 2.06)*	2	[33, 95]
	Levonorgestrel 0.25 mg	JIB	0.55 (0.34, 0.90)‡	6	[94]
	Sirolimus 8 mg	RYGB	0.54 (0.25, 1.17)*	4	[33, 96, 97]
	Hydrochlorothiazide 75 mg	JIB	0.46 (0.33, 0.65)*	4	[98, 99]
	Sertraline 100 mg	RYGB	0.40 (0.19, 0.84)†	5	[100]
	Ampicillin (pivampicillin 750 mg)	JIB	0.37 (0.16, 0.89)†	5	[90]
	Phenytoin 200 mg	JIB	0.32 (0.17, 0.58)†	7	[101]

▲ = Indicating a significant increase in oral drug exposure (AUC, F_{oral} or steady-state concentration) following surgery. — = No statistical significant change in oral drug exposure.

▼ = Significant reduction in oral drug exposure. X = mean ratio change based on geometric mean, GBP, Gastric bypass (gastroplasty and Roux-en-Y gastric bypass); JIB, Jejunoileal bypass; BPD, Biliopancreatic diversion; BPDDS, Biliopancreatic dDivision with a duodenal switch; RYGB, Roux-en-Y gastric bypass; MMF, mycophenolate mofetil. *t-test performed at 5% significance level. †Statistical outcome as reported in publication. ‡Welch's t-test at a 5% significance level.

geometric mean drug exposure ranged from a 10.43 fold increase with a 95% confidence interval (CI) ranging from 0.10 to 1058 ($n = 32$) [34] to a 5.88 fold reduction ($n = 1$) [35] (Table 1) [36–41]. The overall post/pre surgical oral drug exposure ratio (ppR) obtained from meta-analysis significantly diverged from pre surgery with a mean ppR of 0.80 with a 95% CI of 0.67, 0.94 (z value = -2.65 , $P < 0.01$), when analyzing quantitative data providing mean and variance of exposure pre and post bariatric surgery.

Analysis in accordance to the Biopharmaceutics Classification System Classifying drugs into BCS classification, class I (high solubility, high permeability), class II (low solubility, high permeability), class III (high solubility, low permeability) and class IV (low solubility, low permeability), identified eight drugs as BCS class I ($n = 66$ patients), three drugs as BCS class II ($n = 7$), eleven drugs as BCS class III ($n = 53$) and three drugs as BCS class IV ($n = 8$). A total of eight drugs were found to be inconclusive ($n = 40$). Information was lacking in the literature with regards to the BCS classification of pivampicillin, para-aminosalicylic acid and lopinavir/ritonavir.

Of the eight drugs identified as BCS class I, four drugs displayed a reduction in exposure following surgery, four drugs remained unaltered and one drug displayed an increase in drug exposure. Out of eleven mapped BCS class III drugs, five displayed a reduction in drug exposure

following surgery. An additional five drugs displayed unaltered drug exposure, whereas one drug displayed an increase. All BCS class II and IV drugs (total of six) displayed a reduction in drug exposure following surgery (Figure 2).

Analyzing BCS classified drugs where studies provided quantifiable measurements of drug exposure (*i.e.* AUC, F_{oral} and plasma or serum concentrations), combining weighted means and variance of pre/post drug exposure ratio, BCS class I ($n = 5$ drugs, $n = 108$ population) displayed a weighted mean ppR of 0.94 (95% CI 0.66, 1.34). BCS class II ($n = 2$ drugs, $n = 5$ population) displayed a weighted mean ppR of 0.80 (95% CI 0.48, 1.36), BCS class III ($n = 8$ drugs, $n = 111$ population) showed a weighted mean ppR of 0.86 (95% CI 0.68, 1.10), whereas BCS class IV ($n = 2$ drugs, $n = 17$ population) displayed a weighted mean ppR of 0.51 (95% CI 0.22, 1.17). Statistical analysis did not reveal any significant differences from pre surgical ratio of 1 between BCS subgroups ($P > 0.05$) (Figure 3).

Drugs where studies provided quantifiable measurements of drug exposure were further statistically analyzed with regards to $Do \leq 1$, BCS class I and III ($n = 16$ drugs, $n = 262$ population) vs. BCS class II and IV ($n = 4$ drugs, $n = 48$ patients). $Do \leq 1$ drugs displayed a weighted mean ppR of 0.83 (0.69–1.00), whereas $Do > 1$ drugs displayed a ratio of 0.70 (95% CI 0.45, 1.10). Statistical analysis revealed no statistical significance from a pre surgical ratio of 1 or between subgroups ($P > 0.05$) (Figure 4).

Figure 2

Categorical trends (reduced, unaltered and increased) in oral drug exposure in relation to f_a (fraction of orally administered dose absorbed) and Do (dose number) in accordance with the BCS dividing drugs into BCS class I–IV [52,60–89]. Reduced exposure (▼); Unaltered (□); Increased (△).

Figure 3

Log mean post/pre surgery drug exposure ratio of BCS I–IV classified drugs. ○ log mean drug ratio, ● combined log mean ratio and standard deviation of subgroup

Analysis in accordance to main route of elimination
Examining drugs in accordance with the main route of elimination produced a weighted mean ppR in oral drug exposure of 0.83 (95% CI 0.59, 1.17) for CYP3A4/5 substrates ($n = 7$ drugs, $n = 99$ patients), 0.32 (95% CI 0.14, 0.72) for CYP2C substrates ($n = 1$ drug, $n = 16$ population), 0.90 (95% CI 0.68, 1.18) for mainly renally-cleared drugs ($n = 5$ drugs, $n = 103$ population) and 0.76 (95% CI 0.57, 1.01) for the remaining drugs ($n = 8$ drugs, $n = 92$ population). Sta-

Figure 4

Mean post/pre surgery drug exposure ratio and standard deviation in relation to quantitative Do (dose number)

tistical analysis revealed no difference in ppR between the subgroups ($P > 0.05$), whereas the CYP2C subgroup significantly differed from the pre-surgical ratio of 1, displaying a z-value of -2.72 and $P < 0.001$.

Discussion

Evaluation of drug utilization following gastric bypass

The observed practice of altering formulation properties to liquid preparations is considered necessary in health-care due to the postoperative condition of the patient rather than as a proactive measure against altered pharmacokinetics due to changes in GI physiology. Patients are advised to remain on liquid formulations for approximately 2–3 weeks, varying nationally to 3 months to life-long, post bariatric surgery to prevent any unnecessary strain on the gastric and jejunal transection lines and the gastrojejunal anastomosis and therefore to allow time for healing. As an unintentional consequence changing to liquid preparations may result in an increase in oral bioavailability for solubility limited drugs.

Pharmacotherapeutic treatment of type 2 diabetes was ceased in 67% of patients following surgery. The prescription of metformin remained unaltered following surgery, albeit being observed to be significantly reduced 12 months postoperatively, by Malone & Alger-Mayer, following 114 patients up to 24 months post surgery [42].

Antidepressants, TCAs and SSRIs were continued immediately postoperatively in all cases. This was consistent with

the report by Malone & Alger-Mayer, indicating prescriptions of TCAs and SSRIs remained statistically unaltered 12 months post surgery. Vitamin and mineral deficiencies are likely to occur indefinitely in the bariatric patient, resulting in the need for lifelong supplementation [43]. Deficiencies are most likely to occur with fat soluble vitamins (A, D, E and K), calcium and iron. Calcium and iron absorption is highly influenced by the reduction of hydrochloric acid production within the stomach after bariatric surgery [43].

Medication reviews have been performed observing modifications to patient dosing and formulation after bariatric surgery. Currently no consensus guidelines are available regarding considerations of pharmacotherapy post bariatric surgery. Evidence based national guidelines are warranted as bariatric surgery is becoming a more popular method for the treatment of obesity [44].

Oral drug exposure following bariatric surgery

Reviewing current data on changes in drug exposure prior to and post bariatric surgery reveals many uncertainties regarding the prediction of post bariatric surgery drug bioavailability and the mechanisms behind these changes. BCS did not prove to be enough to explain the observed trend.

Post bariatric surgery imposed restrictions on gastric volume (e.g. SG and RYGB) has been observed to reduce the gastric emptying time of liquids [45, 46] and may further lead to an increase in gastric pH [47, 48]. This together with a reduced fluid intake may impact on the solubility of orally administered drugs.

Statistical analysis did not present any significant trends when examining BCS class I-IV, Do or elimination subgroups. None of the $Do > 1$ classified drugs displayed an increase in bioavailability postoperatively, whereas the $Do \leq 1$ group exhibited a larger variability in pre/post surgery drug exposure outcome. This may be due to solubility issues of the $Do > 1$ group, resulting in an overall reduction in oral drug exposure following surgery. The impact is however unclear due to a low number of drugs falling into the $Do > 1$ category, where further clinical data are necessary to establish the case.

Due to the restriction of the gastric volume following certain types of bariatric surgery (e.g. RYGB and BPD-DS) the default concomitant fluid intake of 250 ml in the BCS may no longer be valid. This will have implications for shifting the boundaries between BCS class I/III and II/IV, such that some freely soluble drugs may become solubility limited dependent on the administered dose. This is further complicated by a potentially altered gastric pH [11, 12, 29, 47, 48].

A small intestinal bypass will reduce the absorption area and may also alter the regional distribution and abundance of drug metabolizing enzymes and transporters thus altering exposure of substrate drugs. When examining drugs with respect to the main route of elimination, no significant difference was observed between CYP3A,

CYP2C, renal and other drugs. These results were also associated with a high degree of uncertainty due to scarcity of data, albeit a higher ppR of CYP3A may be expected due to the GI abundance of CYP enzymes where CYP3A4 is the most highly abundant. The bypass of highly abundant regions of CYP3A4 may lead to an increase in oral bioavailability while such an effect may become less relevant for substrates due to decreasingly abundant CYP2C9/19 and CYP2D6. Such a hypothesis may be supported by the observed trend in AUC of atorvastatin acid, mainly metabolized by CYP3A4 [49], thus potentially displaying an increase in bioavailability post malabsorptive bariatric surgery due to the bypass of significant segments of GI regions highly abundant in CYP3A4 [26], whereas this effect may be counteracted by a reduced absorption area. Following BPD-DS a significant increase in AUC of atorvastatin acid (two-fold) was observed, whereas no significant change was observed following RYGB, thus potentially increasing the risk of adverse effects, such as myopathy, following BPD-DS [36, 37, 50].

The lack of quantifiable drug exposure data means that drugs displaying a low f_g or limited absorption prior to surgery are likely to be wrongly classified when trying to generalize over a wide variety of drugs, such as metformin and phenoxymethylpenicillin.

Metformin, a highly soluble and permeability limited basic compound [51, 52], has been suggested to be subject to saturable transporter uptake to some extent by organic cation transporters in the intestine although this is not fully understood, thus resulting in a dose-dependent absorption that is mainly renally-cleared [53, 54]. The observed increase in postoperative bioavailability [55] might be due to altered small intestinal transit; reductions in gastric emptying time and small intestinal motility would in theory lead to a longer exposure time to enterocytic influx transporters. A further reason could be a post surgical alteration in transporter distribution patterns.

Phenoxymethylpenicillin, considered a highly soluble and permeable compound [52], displayed a significant increase in AUC post JIB, possibly due to a reduced intestinal degradation by bacterial β -lactamase due to a major small intestinal restriction [56].

The different surgical implications on GI physiology may result in variable trends in post surgery drug exposure across the range of bariatric procedures, as is the case with atorvastatin acid displaying a significant increase in AUC following the BPD-DS procedure as compared with no significant change following the less malabsorptive RYGB procedure [36, 37]. Also ciclosporin, there was a reduction in drug exposure following JIB, an exclusively malabsorptive procedure [57, 58], as compared with remaining unaltered following the restrictive AGB [59].

The outcomes of oral drug exposure of many commonly prescribed drugs in bariatric surgery populations are still unknown, such as many antidepressants and analgesics. Current available clinical data are very valuable.

Going forward it is important that further clinical studies are designed taking into consideration the potential alterations in concentration–time profiles, relating to pharmacokinetic parameters such as $t_{\max}$. Drugs exhibiting a narrow therapeutic range or displaying less readily measurable clinical endpoints will require more stringent monitoring after bariatric surgery, such as immunosuppressant agents and CNS active drugs.

Due to the multiple physiological factors altered in bariatric surgery (i.e. gastric volume, absorption area, CYP-abundance and regional distribution) [11, 12], and the fact that various drugs might be affected to different degrees by each of these changes, physiologically-based pharmacokinetic (PBPK) modelling may help in elucidating the impact of various bariatric surgeries on different drugs given at different doses. Such an investigation was outside the scope of the current research. However initial attempts on this approach are addressed in another report (Darwich *et al.* submitted and under review) where the complex nature of interplays were manifested.

In conclusion, based on current findings, analysis of general pharmacokinetic parameters alone (i.e. solubility, permeability and main route of elimination) is not enough to explain observed trends in oral drug bioavailability following bariatric surgery, although the findings of this study suggest solubility to potentially play an important role.

These implications support the hypothesis that there are several physiologic and drug-specific parameters which govern the observed changes in drug exposure, thus calling for a more mechanistic approach, integrating all known parameters.

To the authors' knowledge this is the first publication quantitatively examining oral drug bioavailability in relation to a set of pharmacokinetic, biopharmaceutic and other drug-specific parameters and also in the context of pharmacotherapeutic practice following bariatric surgery. Along with further clinical studies, PBPK modelling may provide essential insights into the significance of individual pharmacokinetic parameters and generate important clinical guidance for a constantly growing post bariatric surgery population. Currently, there seems to be no simple algorithm or decision tree that predicts the variable changes to drug bioavailability following bariatric surgery.

Competing Interests

There are no competing interests to declare.

Appendix

Table A1

Controlled trials examining oral drug bioavailability following bariatric surgery

Drug	Surgical procedure	Post/pre surgery drug exposure ratio (mean (95% CI))	Additional information	References
Antimicrobials				
Erythromycin 250 mg	GBP	AUC: 0.61 (0.38, 0.99) ($P > 0.05$)*	Controlled prospective study (n patients = 7)	[92]
Ampicillin (pivampicillin 750 mg)	JIB	F_{oral}0.37 (0.16, 0.89) ($P < 0.05$)*	Controlled prospective study (n patients = 6)	[90]
Sulfisoxazole 1000 mg	JIB	F_{oral}: 0.84 (0.74, 0.94) ($P < 0.05$)†	Controlled prospective study (n patients = 3)	[93]
Phenoxymethyl penicillin 1000 mg	JIB	AUC: 10.43 (0.10, 1058) ($P < 0.05$)†	Controlled prospective study (n patients = 3)	[34]
Cardiovascular drugs				
Digoxin 0.5 mg	JIB	AUC: 0.76 (0.59, 0.97) ($P < 0.05$)*	Controlled study (n patients = 9, n controls = 16)	[38]
Digoxin 0.5 mg daily (First day 1 mg)	JIB	AUC: 0.89 (0.70, 1.14) ($P > 0.05$)*	Controlled prospective study (n pre patients = 5, n post patients = 6)	[39]
Hydrochlorothiazide 75 mg	JIB	AUC: 0.46 (0.33, 0.65) ($P < 0.05$)‡	Controlled study as compared to literature data (n patients = 4, n healthy volunteers = 7)	[98, 99]
Immunosuppressants				
Mycophenolic acid (MPA) 2-1000 mg	RYGB‡	AUC: 0.66 (0.21, 2.06)*	Pilot study as compared to literature data (n patients = 2, 4, 1, n controls =)	[33, 102]
Sirolimus 6 mg		AUC: 0.54 (0.25, 1.17)*		
Tacrolimus 2-4 mg		AUC: ‘Reduced’		
Antiepileptics				
Phenytoin 200 mg	JIB	AUC: 0.32 (0.17, 0.58) ($P < 0.05$)*	Controlled study (n patients = 7, n controls = 9)	[101]
Analgesics				
Paracetamol 1500 mg	JIB	AUC: 1.00 (0.647, 1.54) ($P > 0.05$)†	Controlled prospective study (n patients = 3 at 2.7–3.9 months, 5 at 6.4–34 months)	[34]
Phenazone 15 mg kg ^{−1}	JIB	AUC§: 1.06 (0.81, 1.38) ($P > 0.05$)¶	Controlled study (n patients = 17, n controls = 11)	[91]
Oral contraceptives				
Norethisterone 3 mg Levonorgestrel 0.25 mg	JIB	AUC§: 0.80 (0.39, 1.63) ($P < 0.05$)¶ AUC§: 0.55 (0.34, 0.90) ($P < 0.05$)¶	Controlled study (n patients = 6, n controls = 5)	[94]
Estradiol 4 mg Levonorgestrel 0.125 mg	JIB	‘Unaltered’ ‘Unaltered’	Controlled study (n patients = 12)	[103]
‘Contraceptives’	BPD	‘Reduced’	Observed increase in levels of sex-hormone-binding globulin and reduced levels of dehydroepiandrosterone sulphate. Controlled prospective study (n patients = 40)	[104]
Anti-ulceratives				
Ranitidine 300 mg	BPD	AUC: 1.43 (1.12, 1.81) ($P < 0.05$)†	Controlled study (n patients = 11, n controls = 10)	[40]
Ranitidine 150 and 300 mg	BPD	‘Unaltered’	Controlled study as compared to literature data (n patients = 7)	[41]
Statins				
Atorvastatin acid 20–80 mg	BPD-DS	AUC: 1.85 (0.81, 4.27) ($P < 0.05$)*	Controlled prospective study C_{max} ratio: 2.2 ± 1.7 , t_{max} ratio: 2.3 ± 1.3 (n patients = 10)	[36]
Atorvastatin acid 20–80 mg	RYGB	AUC: 1.43 (1.12, 1.81) ($P > 0.05$)*	Controlled prospective study C_{max} ratio: 1.1, t_{max} ratio: 0.5 (n patients = 12)	[37]
Anti-diabetics				
Metformin 1000 mg	RYGB	AUC: 1.20 (0.91, 1.58) ($P > 0.05$)*	Controlled study (n patients = 16, n controls = 16)	[55]
Antidepressants				
Sertraline 100 mg	RYGB	AUC: 0.40 (0.19, 0.84) ($P < 0.05$)*	Controlled study (n patients = 5, n controls = 5)	[100]
Thyroid blockers				
Propylthiouracil 400 mg	JIB	F_{oral}: 1.09 (0.84, 1.42) ($P > 0.05$)*	Controlled prospective study (n patients = 9)	Kampmann 1984

SD, Standard deviation; GBP, Gastric bypass (gastroplasty and Roux-en-Y gastric bypass); JIB, Jejunoileal bypass; BPD, Biliopancreatic diversion; BPD-DS, Biliopancreatic diversion with a duodenal switch; RYGB, Roux-en-Y gastric bypass; AUC, area under curve; F , bioavailability; SS, mean concentration at steady-state; C_{max} , maximum concentration; t_{max} , time at maximum concentration. *Statistical outcome as reported in publication. † t -test performed at 5% significance level. ‡Pre (sirolimus) and post (tacrolimus and MPA) renal transplant patients. §Welch's t -test at a 5% significance level. ¶Calculated estimate of AUC from report.

Table A2Case reports (*n* patients = 1) on oral drug bioavailability following bariatric surgery

Drug	Surgical procedure	Post/pre surgery drug exposure ratio	Additional information	References
Antimicrobials				
Rifampicin	JIB	Reduced	Following JIB, the rifampicin dose was increased from 600 to 1200 mg in order to reach necessary serum concentrations.	[105]
Isoniazid		Unaltered		
Ethambutol		Unaltered		
Rifampicin	JIB	Reduced	Patient 1: Isoniazid 300 mg – Serum concentration of 3.6 µg ml ⁻¹ at 2 h as compared with reference value of 4–6 µg ml ⁻¹ .	[106]
Isoniazid		Inconclusive	Patient 2: Isoniazid 300 mg – Serum concentration of 8.4 µg ml ⁻¹ at 2 h. Ethambutol 2400 mg – Serum concentration under 1 µg ml ⁻¹ . Rifampicin 600 mg – Serum concentration of 4 µg ml ⁻¹ at 4 h as compared with reference value of 8 µg ml ⁻¹ .	
Ethambutol		Unaltered		
Rifampicin	JIB	Reduced	Four female patients out of one hundred patients undergoing JIB developed tuberculosis.	[107]
Isoniazid		Unaltered	Blood concentrations were obtained from two patients, displaying a reduced concentration of rifampicin, whereas isoniazid and ethambutol remained within therapeutic range (<i>n</i> patients = 4).	
Ethambutol		Unaltered		
Isoniazid	JIB	Unaltered	Isoniazid and ethambutol blood concentration reported to be within the normal range.	[108]
Ethambutol		Unaltered		
Isoniazid	JIB	Reduced	Drugs excreted in faeces as unaltered tablets after oral administration.	[109]
Ethambutol		Reduced		
Para-aminosalicylic acid		Reduced		
Isoniazid	JIB	Unaltered	Serum concentrations equivalent to that observed in healthy volunteers.	[110]
Ethambutol		Unaltered		
Nitrofurantoin	RYGB	Reduced	Intravenous antibiotics administered due to failure of oral drug therapy failed.	[111]
Amoxicillin		Reduced		
Immunosuppressants				
Tacrolimus	JIB R	AUC: 0.53	After JIB R a 1.90-fold increase in AUC was observed.	[112]
Ciclosporin	JIB	SS concentration: 0.41	<i>n</i> patients = 1, as compared with <i>n</i> controls = 6	[57]
Ciclosporin	JIB R	F_{oral}: 0.36	2.78-fold Increase in drug exposure following JIB R.	[58]
Ciclosporin	LAGBD	Unaltered	Standard cyclosporine therapy was successful in the treatment of a post LAGB surgery patient subject to heart transplant.	[59]
Anticonvulsants				
Phenytoin	RYGB	Reduced	Dose strength up to 500 mg did not achieve therapeutic effect (<3 mg l ⁻¹ as compared with a normal range of 10–20 mg l ⁻¹).	[113]
Phenobarbitone	RYGB	Reduced	At a dose of 60 mg bid, serum levels were reduced (9.9 mg l ⁻¹) as compared with normal range (15–41 mg l ⁻¹).	
Phenytoin	JIB	Reduced	Dose increased from 300 to 500 mg in order to achieve therapeutic effect.	[114]
Ethosuximide	JIB	Reduced	Dose doubled in order to achieve therapeutic effect.	
Phenytoin	JIB R	SS concentration: 0.48	JIB R resulted in an increase in SS concentration.	[115]
Antipsychotics				
Haloperidol	RYGB	Unaltered	Dose doubled immediate post surgery to thereafter be lower to pre surgery dose with effective treatment.	[32]
Anti-cancer drugs				
Imatinib mesylate	BPD-DS	SS concentration: 0.17	Plasma concentration of imatinib 400 mg at steady-state reduced from 965 to 166 ng ml ⁻¹ .	[35]
Tamoxifen	RYGB	Reduced	3 case reports (<i>n</i> patients = 3).	[116]
Temozolomide	RYGB	AUC: 1.02	Unaltered drug exposure following surgery at a dose of 190 mg as compared with literature.	[117]
Anti-HIV drugs				
Lopinavir/ritonavir	RYGB*	Increased	An observed increase in plasma concentration in comparison with control patients.	[118]
Thyroid hormones				
Thyroxine	JIB	Reduced	Dose increase required from 0.2 mg to 0.8 mg daily to produce sufficient response.	[119]
Thyroxine	JIB	Reduced	C _{max} ratio: 0.31. JIB R restored to pre surgery drug exposure.	[120]
Thyroxine	JIB R	Reduced	Dose increase required from 0.3 mg to 0.6 mg daily to reach SS sufficient concentration.	[121]

JIB, Jejunioleal bypass; JIB R, Jejunioleal bypass reversal; BPD, Biliopancreatic diversion; BPD-DS, Biliopancreatic diversion with a duodenal switch; RYGB, Roux-en-Y gastric bypass; LAGBD, Laparoscopic adjustable gastric banding; AUC, area under curve; F, bioavailability; SS concentration, mean concentration at steady-state; C_{max}, maximum concentration; t_{max}, time at maximum concentration. *Total gastrectomy followed by an oesophagojejunostomy with a Roux-en-Y reconstruction.

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