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The influence of bypass procedures and other anatomical changes in the gastrointestinal tract on the oral bioavailability of drugs.

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Abstract

The gastrointestinal (GI) tract plays an important role in the absorption of orally administered drugs. However, in some cases the anatomy of the GI tract is changed due to GI surgery, which has the potential of influencing drug bioavailability. In this review, we aim to compile, review, and comment the existing but sometimes fragmented scientific data regarding the impact of GI surgery on the oral bioavailability of drugs. Relevant reports were gathered through the PubMed database from database inception through January 2012. Drugs for which at least one trial or case report suggested a change in oral bioavailability or absorption caused by GI surgery are discussed in detail. Major methodological differences, such as study design, number of subjects and choice of reference group, were observed in the reported studies. Predicting the impact of GI surgery on the oral bioavailability was therefore difficult to perform, even the most sophisticated classification systems could not be used for predicting purposes.

1. INTRODUCTION

During drug development, the oral bioavailability of a drug is usually studied in healthy volunteers and in patients with a normal gastrointestinal (GI) tract. However, once the drug is commercially available, it may also be administered to patients with an anatomically changed GI tract. Changing the anatomy of the GI tract is often the consequence, or even the goal, of surgical treatment options in GI diseases such as GI cancer or morbid obesity. However, irreversible anatomical changes may affect various factors contributing to the bioavailability of oral drugs (e.g. gastric and intestinal pH, the surface area available for absorption, active transport mechanisms for absorption). In the past 40 years, drug bioavailability after GI surgery has been extensively studied in humans. However, the existing data are scattered and sometimes fragmented or limited due to case reports and small clinical trials. In this paper, these data were summarized, reviewed and commented in order to make an attempt to (1) predict the impact of an anatomically changed GI tract on the oral bioavailability of specific drugs and to (2) judge whether dose adjustments are needed in these specific patient populations.

We therefore performed a systematical literature search on the impact of surgical changes in the anatomy of the GI tract on the bioavailability of oral drugs. The absorption of oral drugs may also be affected by surgery in general, because of e.g. fluctuating haemodynamics, physiological shifts, intense metabolic changes, reduced GI motility. However, these temporary influences have been well described elsewhere [1] and fall outside the scope of this review. Also the technical aspects of drug administration procedures in, for example, patients with feeding tubes have been described in detail elsewhere [2,3] and are not part of this review. The main focus in this systematical review will therefore be the long-term influences of an anatomically changed GI tract due to GI surgery.

2. DATA SELECTION

We searched the PubMed database for literature examining the impact of an anatomically changed GI tract on drug bioavailability from database inception through January 2012. Additional references were hand searched from the reference lists of identified articles or relevant reviews. The search was limited to English language articles. This paper discusses both case reports and controlled trials. The studies used for this review were selected from a pharmacokinetic point of view: the primary outcome was absorption or bioavailability. Since the impact on absorption and on bioavailability are different outcomes, two study designs are possible. The oral administration of a drug after the GI tract has been anatomically changed can be compared either to the intravenous administration after GI surgery, or to the oral administration in subjects with a normal GI tract; thereby investigating the impact on absorption and bioavailability, respectively. Articles evaluating only efficacy or safety were excluded.

3. GI SURGICAL PROCEDURES AND THEIR INFLUENCE ON THE DRUG ABSORPTION PROCESS

In order to assess the influence of anatomical changes in the GI tract on oral bioavailability, it is essential to understand the fundamental concepts of oral bioavailability and its contributing factors. The following briefly reflects on some of these fundamentals.

The term “oral bioavailability” is used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action.[4] Because measuring drug concentration at its site of action is complicated in human subjects, most bioavailability studies determine the systemic exposure to the unchanged drug by measuring plasma or serum concentrations of the drug. These concentrations are used to construct a concentration-time curve and systemic exposure is expressed as the area under the concentration-time curve (AUC). Although this parameter is affected by all the pharmacokinetic processes (absorption, distribution, metabolism and elimination), one would expect mainly altered absorption to be responsible for alterations in the AUC after an anatomical change in the GI tract.

The absorption of oral drugs from the GI tract into the systemic circulation is a complex process. The rate (expressed as time to reach maximum concentration, t_{max}) and the extent of absorption depend on several factors. The physical state of the drug (solution, suspension or solid dosage form) is the first factor that affects the drug absorption process. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension or solid form.[5,6] The latter requires disintegration in order to become soluble within the GI environment. This step is promoted by gastric mixing and is often the rate-limiting step in the absorption process. Subsequently, the dissolution of the drug is determined by its water solubility. Lipophilic drugs may therefore need bile acids to enhance their solubility. Also gastric and intestinal pH are important factors influencing ionization and, consequently, drug solubility. The last step in the absorption process is the diffusion of the drug across the GI membranes in order to become available into the systemic circulation. Most drugs are absorbed from the GI tract by passive diffusion favoring the absorption of unionized, lipophilic drugs. Other drugs may require transporters for their absorption. Not only membrane permeability, but also site of absorption, surface area available for absorption, drug concentration and blood flow at the site of absorption and contact time with the GI tract (gastric emptying time and intestinal transit time) are important factors influencing the rate and extent of absorption.[4] Most drugs are absorbed in the proximal small intestine (duodenum and jejunum) because of its large surface area created by the microvilli, its generous blood flow and its permeable mucosa.[5,7] Nevertheless, absorption from other parts of the GI tract is also possible: some weak acids, unionized drugs and lipophilic substances may already be absorbed from the stomach.[8]

During or following absorption from the GI tract, the drug can be metabolized by GI or hepatic enzymes, before it reaches the systemic circulation; this is called first pass metabolism. In addition, some drugs are substrates for P-glycoprotein (P-gp) which hampers absorption by pumping the drug back into the GI tract. All of this is the phenomenon of presystemic elimination. Drugs with a high presystemic elimination consequently have a low systemic exposure and bioavailability.

GI surgical procedures often cause irreversible alterations to the anatomy of the GI tract which may have an impact on the absorption and/or bioavailability of oral drugs.

Taking the several steps of the absorption process of oral drugs into account, changes in (1) GI pH, (2) gastric emptying, (3) intestinal transit time, (4) surface area for absorption and (5) first pass metabolism capacity, are assumed to affect the rate and/or the extent of absorption of oral drugs [6]. In addition, the elimination of drugs (e.g. enterohepatic recirculation) could also be influenced by GI surgery.[9-11] Because both elimination and absorption contribute to the systemic exposure to a drug, changes to one of these processes will obviously alter the bioavailability of a drug. Table 1 summarizes the GI surgical procedures and their possible effects on the bioavailability of oral drugs.

4. ORAL BIOAVAILABILITY OF DRUGS IN PATIENTS WITH AN ANATOMICALLY CHANGED GI TRACT

Table 2 summarizes the selected controlled studies and case reports that have described the impact of an anatomically changed GI tract on the absorption and/or bioavailability of oral drugs. Even though Table 2 gives a complete overview, in the following sections we only focus on those drugs for which at least one trial or case report suggested a change in oral bioavailability or absorption caused by GI surgery.

4.1. Analgesics

The most important absorption site of paracetamol has been suggested to be the jejunum distal to the duodenojejunal flexure.[17] This implies that bypassing or removing this part of the jejunum could result in malabsorption of paracetamol after oral administration and consequently in a reduced bioavailability. In fact, AUC values observed after oral administration in patients with a duodenostomy or a jejunostomy (ranging from 15 cm to 60 cm distal from the duodenojejunal flexure) (n = 5) were significantly lower compared to those observed in healthy volunteers with a normal GI tract (n = 32).[17] In addition, pylorus preserving pancreatoduodenectomy (PPPD) (n= 12) and jejunoileal bypass (JIB) (n = 3) (both preserving the duodenojenunal flexure) had no impact on the bioavailability of oral paracetamol.[17,19] Even administration of paracetamol as an oral elixir through a jenunostomy tube (n = 2) resulted in similar pharmacokinetic parameters as in healthy volunteers with a normal GI tract (n = 4).[20]

The rate of absorption of paracetamol appears to depend on gastric emptying time.[64] Partial (n = 7) and total gastrectomies (n = 5) accelerate gastric emptying, resulting in a shorter t_{max} and a higher C_{max} for oral paracetamol. Although it is more rapidly absorbed from the GI tract, gastrectomy has no clinically relevant impact on the systemic exposure to paracetamol since AUC values were similar to those in healthy volunteers with a normal GI tract (n = 32).[17]

4.2. Cardiovascular drugs

4.2.1. Digoxin

Absorption of oral digoxin primarily occurs in the proximal small intestine (i.e. duodenum and jejunum) [5], and resections of various amounts of the ileum (n = 14) demonstrated to have no impact on the bioavailability of digoxin compared to that in healthy volunteers with a normal GI tract (n = 16).[24] Additionally, JIB surgery, which bypasses a part of the jejunum and ileum, does not necessarily affect the bioavailability of digoxin; the length of the remaining jejunum and the preservation of intestinal continuity with the large intestine seemed to play a major role in the absorption process. The lack of intestinal continuity due to an end-jejunostomy appears to result in ineffective serum levels in 1 patient.[26] Furthermore, Marcus et al. [23] reported no significant differences in AUC values before and after JIB surgery with 300mm of jejunum left (n = 7), whereas in a study of Gerson et al. [24] a reduced bioavailability of digoxin was observed in 5 of 9 patients with JIB compared to healthy subjects with a normal GI tract (n = 16). Those patients with the most decreased AUC values had only 250 to 263 mm of jejunum left after JIB surgery. In fact, Gerson et al. [24] found a strong correlation between the length of the remaining jejunum and the bioavailability of digoxin. A reduced bioavailability however may still result in therapeutic levels of digoxin.[25,65] Nevertheless, since digoxin has a small therapeutic range [66], therapeutic drug monitoring of digoxin may be recommended in patients with an anatomically changed GI tract.

4.2.2. Quinidine

It would be expected that an increased gastric pH results in a reduced ionization of the basic drug quinidine and, consequently, in a better absorption due to a larger fraction unionized quinidine. In contrast, in patients with gastrectomy combined with vagotomy (n = 10), the serum quinidine levels were significantly reduced at all times of observation during the 6-hour experiment compared to the levels obtained before surgery.[27] However, it should be mentioned that the postoperative serum levels were still rising at 6 hours postdose, while preoperative serum levels reached a maximum at 2 – 4 hours postdose. Therefore, it can only be concluded that the rate of absorption of quinidine is reduced after gastrectomy with vagotomy.[27] In the same study, no differences were found in the serum levels pre- and postoperatively in patients with only partial gastrectomy (n = 2).[27] Due to these limited data, it is difficult to predict the impact of GI surgery on the bioavailability of oral quinidine.

4.2.3. Atenolol and propranolol

Like quinidine, a better absorption after an increase of gastric pH could theoretically be expected for the basic drugs atenolol (pKa 9.6) and propranolol (pKa 9.5). However, the rate of absorption (expressed as t_{max}) and the systemic exposure to atenolol (expressed as AUC) in patients with partial gastrectomy (n = 29) were comparable to those of healthy control subjects (n = 18), indicating that partial gastrectomy had no impact on the bioavailability of oral atenolol.[14]

Theoretically, the absorption of propranolol should also be improved due to an increase in gastric pH; however, the opposite was observed in patients with partial gastrectomy. In contrast to atenolol, systemic exposure to propranolol in these patients (n = 29) was significantly lower compared to that in healthy subjects with a normal GI tract (n = 18).[14] The observed difference in impact of partial gastrectomy on the bioavailability of atenolol and propranolol was suggested to be due to their different physicochemical properties, atenolol being hydrophilic and propranolol lipophilic). Leth et al. [67] observed a 70% reduction in excretory pancreatic function after partial gastrectomy and a subsequent reduction of lipid absorption. The authors [14] hypothesized that this observation was in

line with the reduced absorption of the more lipophilic propranolol. In contrast, partial gastrectomy combined with vagotomy (n = 4) did not reduce the systemic exposure to propranolol; systemic exposures were even similar to those obtained before surgery.[13] In addition, patients with only vagotomy (n = 7) also had a comparable systemic exposure to that before surgery.[13] Although systemic exposure was not altered in both these patients groups, the rate of absorption differed between these groups. The absorption was significantly slower after vagotomy compared to that before surgery, whereas the rate of absorption remained normal in patients after vagotomy combined with partial gastrectomy.[13] Delayed gastric emptying, as a result of vagotomy, was probably compensated by the impact of partial gastrectomy on gastric emptying time.

In conclusion, these studies [13,14] are not consistent and several factors such as lipophilicity and gastric emptying time seem to influence the absorption of propranolol.

4.2.4. Hydrochlorothiazide

Despite an intact duodenum and upper jejunum (the major site of absorption of hydrochlorothiazide), a 50% decrease in systemic exposure to hydrochlorothiazide was observed in 5 patients after JIB surgery [28] when compared to previously reported AUC values of 8 healthy subjects with a normal GI tract. The investigators suggested that absorption of the drug occurred almost normally but that the time period for absorption was not long enough due to a shorter intestinal transit time. These findings should be interpreted with caution since the AUC values used as a reference for subjects with normal GI tract were obtained by another group of investigators and group characteristics were not matched (e.g. different mean bodyweight and different number of subjects).

4.2.5. Atorvastatin

Atorvastatin has a variable and complex intestinal and hepatic first pass metabolism. It is not only metabolized enzymatically by CYP3A4 and CYP3A5, whose expression is highest in the duodenum, but it is also a substrate for P-glycoprotein. Bypassing a large part of the small intestine, and particularly the duodenum, may therefore result in an altered bioavailability of atorvastatin. In fact, both biliopancreatic diversion (BPD) with duodenal switch (n = 10) [30] and gastric bypass (n = 12) [29] had a variable but significant impact on the systemic exposure to atorvastatin. This impact showed to be associated with the presurgical first pass metabolism capacity of the GI tract. Nine patients with a high first pass metabolism of atorvastatin and consequently a low systemic exposure prior to surgery showed a median 1.2-fold increase in systemic exposure to atorvastatin after gastric bypass surgery, whereas in 3 other patients with a low first pass metabolism before surgery, a median 2.6-fold reduced systemic exposure was observed compared to that before surgery.[29] Because the anatomy of the GI tract after BPD with duodenal switch has been changed more drastically, the impact of this surgical procedure on the bioavailability of atorvastatin is even more apparent than after gastric bypass surgery. Here, a significant mean 2-fold higher systemic exposure to atorvastatin was observed after BPD with duodenal switch compared to that before surgery.[30] As a consequence, lower effective doses of atorvastatin should be used in these patients.

4.3 Drugs for the central nervous system

For phenytoin, a high interindividual variability in its pharmacokinetics and a narrow therapeutic range have been described.[68] Therefore, caution is recommended when phenytoin is administered orally in patients with an anatomically changed GI tract. In a controlled study, the bioavailability of phenytoin was proven to be significantly reduced after JIB surgery (n = 7) compared to control subjects with a normal GI tract (n = 9).[33] Peterson and Zweig moreover reported a patient who had recurrent seizures several weeks after JIB surgery and who also required higher doses of phenytoin and ethosuximide to maintain successful therapy.[34] Although no controlled study evaluated the influence of gastric bypass on the bioavailability of oral phenytoin, one case was reported of a patient with undetectable phenytoin levels after gastric bypass surgery despite the administration of high doses.[35] Therefore, patients with an anatomically changed GI tract should be carefully monitored when phenytoin is given orally. Even intravenous administration might be considered.

4.4 *Hormones and related compounds*

4.4.1 Metformin

It was hypothesized that bypassing the major absorption site of metformin (i.e. duodenum and jejunum) would reduce its oral bioavailability. In contrast, a trend towards increased metformin absorption and bioavailability was observed in 16 nondiabetic post-gastric bypass patients compared to 16 healthy controls.[37] The investigators suggested several factors that could explain the increased systemic exposure to metformine after gastric bypass surgery. Metformin absorption is transporter dependent and saturable. Preventing saturation of these transporters by decreasing the rate at which the drug enters the small intestine (e.g. delayed gastric emptying because of gastric bypass surgery) could therefore result in a higher systemic exposure. Also upregulation of these transporters may occur after changing the anatomy of the GI tract. Consequently, decreasing the surface area for absorption does not necessarily reduce the bioavailability of drugs.

4.4.2 Thyroxine

One case report described inadequate therapeutic levels after JIB surgery and 3-fold higher doses were needed in this patient for the treatment of hypothyroidism [39,69]; but no controlled studies are available that describe the impact of an anatomically changed GI tract on the absorption or bioavailability of the thyroid hormone thyroxine.

4.4.3 Oral contraceptives

Fertility is often improved by weight loss after bariatric surgery.[70] Furthermore, due to the possible nutritional deficiencies caused by bariatric surgery, pregnancy should be avoided during the rapid weight loss period, that is for at least 1 year after surgery.[70,71] It is therefore important to know whether an anatomically changed GI tract may affect the bioavailability of oral contraceptives.

Only 2 controlled studies evaluated the impact of JIB surgery on the pharmacokinetics of oral contraceptives.[40,41] Victor et al. [41] reported lower plasma levels of norethisterone and levonorgestrel in patients with JIB (n = 6). However, this decrease was only statistically significant for levonorgestrel during the absorptive phase (at 2, 4 and 6h after administration) compared to the levels of 5 healthy non-obese women with a normal GI tract.[41] Andersen et al. [40] found no evidence for malabsorption of levonorgestrel, oestradiol and oestrone after JIB surgery (n = 12). On the contrary, in this study levonorgestrel levels were significantly higher after JIB surgery compared to those of morbidly obese

women before surgery (n = 6). According to Andersen et al. [40], there is a reasonable explanation for this increase in plasma levels of levonorgestrel after surgery. They found a significant negative correlation between peak levels and body weight suggesting that obesity, and not intestinal bypass, may affect the levonorgestrel levels. Women had low levonorgestrel levels because of obesity, but after major weight loss due to JIB surgery, levonorgestel levels were increased. This hypothesis however was not confirmed by a pharmacokinetic study of Westhoff et al.[72] They evaluated the systemic exposure and peak levels of ethinyl oestradiol and levonorgestrel in obese women and compared the values with those of healthy normal-weight controls. Here, the differences in systemic exposure and peak levels were not statistically significant for levonorgestrel, while a significant lower systemic exposure and lower peak levels of ethinyl oestradiol were observed in the obese women compared to the normal-weight controls. This, again, indicates the influence of a control group on the interpretation of the results. Both studies [40,41] included women with a normal GI tract as control group, but the mean bodyweight of the both control groups differed substantially. The control group of Andersen et al. consisted of morbidly obese women who were studied before JIB surgery, whereas Victor et al. used non-obese women as a reference group. Taking these 2 studies into account, a negative impact of JIB surgery on the bioavailability of oral contraceptives can not be excluded.

The absorption of oral levonorgestrel has also been evaluated in patients with an end-ileostomy. Nilsson et al. [16] reported slightly lower levonorgestrel levels in patients who had undergone proctocolectomy with a conventional ileostomy (n = 5), while patients with a continent ileostomy reservoir (n = 10) achieved significantly lower levels compared to those of healthy control subjects (n = 5 and n = 4, respectively).[16] The lack of a colon and consequently the lack of normal bacterial flora could be responsible for the observed decrease in absorption since the absorption of levonorgestrel is influenced by bacteria. Additionally, the absolute bioavailability of levonorgestrel and ethinyloestradiol in patients with an end-ileostomy was investigated by Grimmer et al.[15] After intravenous administration of levonorgestrel, a significantly higher AUC was observed in patients with an ileostomy (n = 5) compared to healthy controls (n = 5). The opposite was found for intravenous ethinyloestradiol for which the AUC was significantly lower in patients with an ileostomy. The same trends were seen after oral administration. Nevertheless, the absolute bioavailability in patients with an ileostomy was comparable to that in the healthy control subjects. The authors found no apparent explanation for this phenomenon. Unlike levonorgestrel, ethinyloestradiol exhibits enterohepatic recirculation which requires the presence of bacterial flora. One could hypothesize that, due to the lack of a colon in patients with an ileostomy, part of the drug cannot be reabsorbed resulting in a lower AUC.

In conclusion, evidence regarding a reduced bioavailability of oral contraceptives is quite limited in patients with an anatomically changed GI tract. Furthermore, none of the observed lower plasma levels of oral contraceptives after GI surgery were below the minimal level required to ensure ovulation inhibition. Some of these lower plasma levels were even comparable to those found in healthy women taking lower-dose pills. Consequently, a good efficacy could be achieved with the normal-dose pills even if the systemic exposure to oral contraceptives is reduced due to GI surgery. Nevertheless, it seems advisable to avoid lower-dose pills in patients with an anatomically changed GI tract. Information regarding evidence on the safety and efficacy of oral contraceptives in women who had undergone bariatric surgery for obesity can be found in a systemic review of Paulen et al.[70]

4.5 Immunosuppressants

4.5.1 Sirolimus, tacrolimus and mycophenolic acid

According to a study of Rogers et al. [42], the systemic exposure to sirolimus (n = 4), tacrolimus (n = 5) and mycophenolic acid (n = 5) tends to be reduced after gastric bypass surgery compared to patients with a normal GI tract, but a statistical test was not performed. Although their results have been dose-normalized, it should be emphasized that these results were compared to previously published exposure data in the non-bypass population using different doses and formulation forms, suggesting that the control group used may be unsuitable for comparison. Nevertheless, because of the narrow therapeutic range and interindividual variability in blood concentrations, therapeutic monitoring is required and the risk of a reduced bioavailability after GI surgery should be kept in mind.

4.5.2 Cyclosporine

Because bile enhances the absorption of cyclosporine [73], GI surgical procedures that affect bile secretions (e.g. gastric bypass) are likely to influence the bioavailability of cyclosporine. This hypothesis has been confirmed by Marterre et al. [43]; in order to maintain similar trough cyclosporine levels, higher doses of cyclosporine were required in 3 patients after gastric bypass compared to those before surgery.[43] Reduced cyclosporine levels were also observed in 2 patients after JIB.[44,45]

4.6 Antimicrobial – antiviral drugs

4.6.1 Moxifloxacin

The absorption of oral moxifloxacin was not affected in 12 patients who had undergone gastric bypass surgery [46]: the exposure to moxifloxacin was found to be equivalent for oral and intravenous administration after gastric bypass surgery, indicating that the absolute bioavailability is similar to that in subjects with a normal GI tract. However, these exposure data seemed to be higher for both administration routes compared to previously published data in healthy volunteers without a gastric bypass. This suggests that the elimination phase (e.g. enterohepatic recirculation) is likely to be affected by the anatomical changes in the GI tract. Nevertheless, this study was not designed to provide insight into the other pharmacokinetic processes and therefore, statistical confirmation of a changed elimination was not possible.

4.6.2. Sulfafurazole and sulfamethazine

Since sulfafurazole is an acidic sulfonamide, a reduced absorption was suggested after GI surgical procedures that increase gastric pH. Despite the fact that sulfafurazole serum levels were decreased in patients with a gastrectomy combined with vagotomy (n = 10), patients with only partial gastrectomy (n = 2) unexpectedly achieved similar levels as before surgery.[27] Like quinidine (described in section 4.2.2), the postoperative serum levels in patients with gastrectomy combined with vagotomy were also still rising at 6 hours postdose, while preoperative serum levels reached a maximum at 2 – 4 hours postdose. The absorption phase of sulfafurazole therefore seems to be prolonged in patients with gastrectomy combined with vagotomy. Similarly, the absorption of sulfamethazine (also an acidic sulfonamide) was delayed (but not reduced) in patients with gastrectomy combined with vagotomy (n = 4).[12] The absorption in patients with only vagotomy (n = 4) however was not impaired.[12] Taking these studies into account, changes in absorption are more

likely attributed to the association of vagotomy with partial gastrectomy. In addition, JIB surgery had no impact on the oral bioavailability of sulfafurazole.[47]

4.6.3. Penicillin

Penicillin exhibits a large first pass metabolism. Reducing this first pass metabolic capacity by bypassing a large part of the small intestine will definitely increase the bioavailability of oral penicillin. In fact, higher AUC values were achieved after JIB surgery (n = 3) compared to those before surgery.[19]

4.6.4. Ethambutol, isoniazid and rifampicin

The bioavailability data of the antituberculosis agents ethambutol, isoniazid and rifampicin after GI surgery are rather fragmented and limited to case reports of patients after JIB surgery. Although therapeutic levels of ethambutol and isoniazid were achieved in most patients [48-52], rifampicin levels were lower after JIB [49,50,52]. Only one patient was reported to have lower ethambutol levels.[50] These observations, however, were never confirmed by a controlled study in patients with JIB. The absorption of oral ethambutol has also been described in patients with vagotomy and partial gastrectomy.[27] The latter (n = 2) did not modify the absorption, whereas malabsorption was found in patients with vagotomy in combination with partial gastrectomy (n = 10).

4.6.5. Lopinavir

The serum/plasma levels of lopinavir have been studied in 2 different patients with an anatomically changed GI tract. One patient with total gastrectomy achieved lopinavir levels that were comparable to previously reported effective levels.[53] Moreover, Kamimura et al. [54] reported a patient with a percutaneous jejunal tube due to duodenal stenosis. Lopinavir was consequently administered through this jejunostomy tube, but ineffective concentrations of lopinavir were obtained. In contrast, removing the jejunostomy tube and performing a gastrojejunal bypass resulted in effective serum levels. This surgical procedure preserved a larger part of the jejunum which appeared to be an important absorption site for lopinavir.

4.6.6. Acyclovir

Although no controlled studies were performed to evaluate the impact of GI surgery on the bioavailability of oral acyclovir, there is one case report that showed reduced plasma levels of acyclovir after oral administration in a patient with terminal ileal resection.[55]

4.7. Antitumoral drugs

Patients who underwent GI tumor resections may additionally require anticancer therapy after surgery. Investigating the impact of GI surgery on the bioavailability of antitumoral drugs is therefore vital.

4.7.1. Tegafur

Two controlled studies demonstrated that the systemic exposure to oral tegafur after gastrectomy (n = 26 and n = 12) was comparable to that before surgery [59,60], indicating that gastrectomy has no impact on the bioavailability of this drug.

4.7.2. Imatinib

Oral administration of imatinib in patients with an anatomically changed GI tract seemed to result in a reduced bioavailability. In one patient with BPD with duodenal switch, plasma through levels were measured before and after surgery and a 83% reduction was observed postoperatively, resulting in inadequate levels.[62] Additionally, the trough concentrations of imatinib after gastric bypass surgery were also reduced, although treatment with imatinib was successful in this one patient.[61]

4.7.3. Temozolomide

One case report described the failure of oral therapy with temozolomide in a patient who had previously undergone gastric bypass surgery.[63] Temozolomide plasma concentrations were measured in order to explain this inadequate therapy, but these plasma levels were consistent with values reported for patients with a normal GI tract, indicating that failure of therapy was not due to an anatomically changed GI tract.

4 CONCLUSION

Although many studies have examined the impact of an anatomically changed GI tract on the oral bioavailability of drugs, this review confirms that this impact is drug-specific and complicated by many factors. Not unexpectedly, the effect of GI surgery on the bioavailability was independent from the pharmacological properties of the drugs studied.

Since solubility and permeability of a drug are important factors that determine the rate and extent of drug absorption, using the Biopharmaceutical Classification System could provide a better insight in the influence of GI surgery on the absorption and, consequently, on the oral bioavailability of drugs. However, it turns out that the impact on absorption is not biopharmaceutical class-specific. Many other factors such as active transporter mechanisms and first pass metabolism should be taken into account when drug absorption and oral bioavailability are studied. Classifying the drugs according to the Biopharmaceutical Drug Disposition Classification System could therefore be useful as a first tool to estimate the risk of changed drug absorption and/or bioavailability after GI surgery. Although this classification system was not developed to predict drug absorption and/or bioavailability, this system incorporates elimination routes, transporter-effects, transporter-enzyme interplay and post absorption transporter effects.[74] Unfortunately, our efforts to classify the drugs according to this system have not revealed any class-specific effects as a result of the different GI surgical procedures.

One could argue that, for some drugs, the available evidence for an altered bioavailability after GI surgery is restricted to case reports and small sample size studies. In addition, some of the discussed surgical procedures (e.g. vagotomy, JIB, BPD) are nowadays less performed or even largely outdated. Nevertheless, these surgical procedures as well as case reports could provide interesting information and are indicative for further research or for other types of GI surgery.

In conclusion, the impact of an anatomically changed GI tract on the oral bioavailability of drugs is an individual drug related matter. Further research to examine this impact is required for each drug separately. In order to investigate the impact of a purely anatomically changed GI tract, the choice of appropriate controls as comparison group seems to be vital for the interpretation of the results. The

control group should have the same characteristics such as bodyweight, sex and medical condition (healthy or treated for the same disease) as the test group. Therefore, studying the same subjects before and after intervention seems to be the most ideal situation.

This review focused on the impact of an anatomically changed GI tract on the bioavailability of drugs, and not on efficacy. Even though there is a good correlation between systemic exposure and efficacy for most drugs, a reduced bioavailability does not necessarily result in an inadequate therapy. Nevertheless, evaluating the bioavailability of oral drugs in patients with an anatomically changed GI tract may be a first step in estimating the risk of unsuccessful therapy in this patient population. Academic centers, investigators and grant-funding bodies should address these complications in order to assist clinicians by presenting guidelines for oral drug dosing in this specific patient population.

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