Exploring optimal pharmacotherapy after bariatric surgery: where two worlds meet

Yska, Jan Peter

9
CHAPTER

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

INTRODUCTION

Worldwide overweight and obesity are a growing problem. For morbid obesity bariatric surgery is currently considered the most effective treatment option. Bariatric surgery results in greater improvement in weight loss outcomes and obesity associated comorbidities compared with non-surgical interventions, regardless of the type of surgical procedure used [1]. In the past years the number of bariatric procedures performed worldwide has been increasing steadily to 468,609 in 2013 [2].

Patients undergoing bariatric surgery have excess weight, often accompanied by multiple comorbidities, such as cardiovascular diseases, type 2 diabetes mellitus, obstructive sleep apnea, osteoarthritis, and depression. Patients may use various medications for those comorbidities. After bariatric surgery the improvement or resolution of comorbidities might lead to changes in pharmacotherapy. Moreover, depending on the type of surgical procedure, after bariatric surgery, drug absorption may be reduced, leading to alterations in pharmacokinetic parameters, affecting pharmacotherapy [3]. On the borderline, where bariatric surgery meets clinical pharmacy, physicians and pharmacists should be prepared to provide optimal pharmacotherapy. However, so far little is known on the effectiveness and safety of pharmacotherapy after bariatric surgery. The objective of this thesis is to explore optimal pharmacotherapy after bariatric surgery.

First, we focused on (pharmaco)epidemiology. To establish what is already known about the changes in pharmacotherapy after bariatric surgery, we conducted a literature review on the influence of bariatric surgery on the use and pharmacokinetics of some frequently used drugs. Then, we carried out two (pharmaco)epidemiological studies on the influence of bariatric surgery on the use of medication, as well as the metabolic effects of different types of bariatric surgery as expressed in complete discontinuation of glycemic therapy for remission of type 2 diabetes mellitus (T2DM), one of the most prominent comorbidities of morbid obesity. Next, an intervention to reduce the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after bariatric surgery as an attempt for optimization of pharmacotherapy, is described. The last part of the thesis investigates the bioavailability of metoprolol, one of the most frequently used drugs before and after bariatric surgery. The influence of Roux-en-Y gastric bypass (RYGB) on the bioavailability of metoprolol from several oral tablet formulations, as studied in vitro as well as in vivo, is addressed.

EXPERIMENTAL RESULTS

In section II of this thesis, focusing on (pharmaco)epidemiology, we present a review of the current literature to evaluate the influence of bariatric surgery on the use and pharmacokinetics of some frequently used drugs (**chapter 2**). Literature was included on the influence of bariatric surgery on pharmacoepidemiology and pharmacokinetics. Drug classes to be searched for were antidepressants, antidiabetics, statins, antihypertensive agents, corticosteroids, oral contraceptives and thyroid drugs. A reduction in the use of medication by patients after bariatric surgery has been reported for various drug classes. Very few studies have been published on the influence of bariatric surgery on the pharmacokinetics of drugs. After bariatric surgery, theoretically, reduced drug absorption may occur. Correct dosing and choosing the right dosage form for drugs used by patients after bariatric surgery are necessary for optimal pharmacotherapy.

Section II also includes the results of two (pharmaco)epidemiological studies. Bariatric surgery can influence the prevalence and incidence of comorbidities, as well as the pharmacokinetics of drugs. This might lead to changes in the use of drugs. Individual changes in pharmacotherapy after bariatric surgery may be caused by improvement or resolution of comorbidities and alterations in pharmacokinetics of drugs. After bariatric surgery, the use of medication may be continued or stopped, and the dosage or dosage formulation may be changed because of adverse drug events or to achieve an optimal therapeutic effect. In **chapter 3** we conducted a study to assess the influence of bariatric surgery on the use of medication in patients before and after surgery, focusing on type, number of medications, and daily dosage. In a combined retrospective and prospective observational study, drug dispensing data from pharmacies of patients undergoing their first bariatric surgery was collected. Dispensing data from 1 month before until 12 months after surgery were analyzed. Drugs were classified according to the WHO-ATC classification system. Dosages of drugs were compared using defined daily dose (DDD). Among 450 patients 12 months after surgery, the mean number of drugs per patient for antidiabetics, drugs acting on the cardiovascular system, anti-inflammatory and antirheumatic drugs, and drugs for obstructed airway diseases decreased by, respectively, 71.3, 34.5, 45.5 and 33.1%. Patients used lower median DDD of oral antidiabetics, beta-blocking agents, and lipid-modifying drugs. We concluded that for some major drug classes 12 months after bariatric surgery, the use of drugs decreased in terms of mean number per patient. A reduction in dose intensity was observed for oral antidiabetics, beta blocking agents, and lipid-modifying drugs. However, after restrictive procedures, decreases were smaller. Dispensing data from pharmacies may provide detailed information on the use of medications by patients after bariatric surgery.

Chapter 4 concerns an observational study on the remission of type 2 diabetes mellitus (T2DM) after different types of bariatric surgery, based on data from general practice. For this study we used data from a very large UK primary health care database, the Clinical Practice Research Datalink (CPRD). The CPRD consists of the computerized medical records of 10 million patients under the care of general practitioners in the United Kingdom. We assessed the effect of different types of bariatric surgery in patients with T2DM on diabetes remission compared with matched control patients, and the effect of the type of bariatric surgery on improvement of glycemic control and related clinical parameters. Remission was defined as a complete discontinuation of antidiabetic medication and normalization of hemoglobin A_{1c} levels. A retrospective cohort study was conducted within the CPRD involving 2978 patients with a record of bariatric surgery (2005-2012) and a BMI of 35 or greater. We identified 569 patients with T2DM and matched them to 1881 patients with diabetes without bariatric surgery. Data on the use of medication and laboratory results were evaluated. Among patients undergoing bariatric surgery, we found a prevalence of 19.1% for T2DM. Per 1000 person-years, 94.5 diabetes mellitus remissions were found in patients who underwent bariatric surgery compared with 4.9 diabetes mellitus remissions in matched control patients. Patients with diabetes who underwent bariatric surgery, had an 18-fold increased chance for T2DM remission, compared with matched control patients. The greatest effect size was observed for gastric bypass (adjusted RR, 43.1), followed by sleeve gastrectomy (adjusted RR, 16.6), and gastric banding (adjusted RR, 6.9). Body mass index and triglyceride, blood glucose, and hemoglobin A_{1c} levels sharply decreased during the first 2 years after bariatric surgery.

Population-based data show that bariatric surgery strongly increases the chance for remission of T2DM. Gastric bypass and sleeve gastrectomy have a greater effect than gastric banding. Although the risks and possible adverse effects of surgery should be weighed against its benefits, bariatric surgery and, in particular, gastric bypass or sleeve gastrectomy may be considered as new treatment options for T2DM.

Section III of this thesis addresses optimization of pharmacotherapy after bariatric surgery. Use of NSAIDs should be avoided in bariatric surgery patients, because they have been implicated in the development of anastomotic ulcerations and perforations. If use of an NSAID is inevitable, a proton pump inhibitor (PPI) should also be used. In **chapter 5**, a randomized controlled intervention study is presented to determine the effect of an, compared to care-as-usual, additional intervention to reduce NSAID use in patients who underwent bariatric surgery, and to determine the use of PPIs in patients who use NSAIDs after bariatric surgery. Patients were randomized to an intervention or a control group. The intervention consisted of sending a letter to patients and their general practitioners on the risks of use of NSAIDs after bariatric surgery and the importance of avoiding NSAID use. The control group received care-as-usual. Dispensing data of NSAIDs and PPIs were collected from patients' pharmacies: from

a period of 6 months before, and from 3 until 9 months after the intervention. Two hundred forty-eight patients were included (intervention group: 124; control group: 124). The number of users of NSAIDs decreased from 22 to 18% in the intervention group and increased from 20 to 21% in the control group (NS). The use of a PPI with an NSAID rose from 52 to 55% in the intervention group, and from 52 to 69% in the control group (NS). We concluded that informing patients and their general practitioners by letter, in addition to care-as-usual, is not an effective intervention to reduce the use of NSAIDs after bariatric surgery. A more successful policy to decrease the use of NSAIDs after bariatric surgery has yet to be found.

Section IV of this thesis focuses on the bioavailability of metoprolol. In **chapter 3** we reported a significant reduction in use of beta blockers after restrictive-malabsorptive weight loss procedures, such as RYGB. However, after surgery a considerable number of patients still use a beta blocker. Metoprolol is a widely used beta blocker, available as immediate and controlled release tablet. Although not evidence based, it is generally recommended to avoid controlled release drug formulations after bariatric surgery [10]. For these reasons we chose to study the bioavailability of metoprolol from immediate and controlled release tablets.

The RYGB is the most commonly performed bariatric procedure, greatly reducing the stomach size and bypassing the duodenum and proximal jejunum. Hence, RYGB may reduce the absorption and bioavailability of oral medications, especially modified release products. Possible variations in bioavailability of orally administered drugs after RYGB may be caused by changes in release of the active compound from the oral tablet formulations. Formulation of oral medication may then be critical to ensure adequate absorption after bariatric surgery. However, results from pharmacokinetic studies are sparse. An in vitro dissolution method simulating conditions before and after RYGB might be a valuable tool to predict the pharmaceutical availability of drugs frequently used by patients after RYGB. In **chapter 6** we describe the development of a gastrointestinal simulation system (GISS), mimicking conditions before and after RYGB, for investigating dissolution characteristics of oral medications. The GISS enables variation in parameters which are relevant to drug release in vivo: pH, volume, residence time, osmolality and agitation. During the test an oral drug formulation in a vessel with a rotating paddle at a temperature between 30-37 °C is exposed to solutions simulating the subsequent parts of the gastrointestinal tract, in fasting and non-fasting conditions, before and after RYGB. Metoprolol tartrate 100 mg immediate-release (IR) tablets and various metoprolol controlled-release (CR) tablets were tested. Release profiles were determined by measuring the concentrations of metoprolol spectrophotometrically. From IR tablets, under all conditions applied, >85% of metoprolol was released within 25 minutes. From all tested CR tablets >90% of metoprolol was released after 22 hours. All the tablet formulations of metoprolol tested showed adequate dissolution, implying that in patients after RYGB no problems

in pharmaceutical availability should be expected. This GISS is a robust dissolution system to assess pharmaceutical availability, simulating fasting and non-fasting conditions before and after RYGB.

To study pharmacokinetics of metoprolol and its metabolite α-hydroxymetoprolol a convenient and accurate method of analysis is necessary. The objective of **chapter 7** was to validate a simple, sensitive LC-MS method to quantify metoprolol and α-hydroxymetoprolol in human serum for application in pharmacokinetic studies. We validated a method on an LC system with an Exactive® Orbitrap mass spectrometer as detector and isotope-labelled metoprolol-d7 as internal standard. Validation showed the method to be accurate, selective and with a good precision. This validated LC-Orbitrap MS analysis for metoprolol and α-hydroxymetoprolol can be used for application in human pharmacokinetics.

In **chapter 8,** we performed an explorative, two-phase, single oral dose pharmacokinetic study of metoprolol in female patients 1 month before and 6 months after RYGB. The aim of this study was to assess the effect of RYGB on the bioavailability of metoprolol from immediate (IR) and controlled-release (CR) tablets. After intake of either 100 mg of metoprolol IR or CR tablet serum concentration-time profiles of metoprolol were determined. The endpoint was the ratio of AUC_{after}/AUC_{before} of metoprolol. Twelve patients were included in the study (metoprolol IR: 7; metoprolol CR: 5). After intake of a metoprolol IR tablet large intra- and interindividual differences for AUC of metoprolol before and after surgery were observed (range ratio $AUC_{0\text{-}10h\ after}/AUC_{0\text{-}10h\ before}$: 0.74-1.98). For metoprolol CR tablets a reduction in bioavailability of metoprolol was observed after surgery (range ratio $AUC_{0\text{-}24h\ after}/AUC_{0\text{-}24h\ before}$: 0.43-0.77). We concluded that RYGB may influence the bioavailability of metoprolol from an IR tablet. The magnitude of changes in bioavailability after RYGB requires close monitoring of patients using metoprolol IR tablets and dose adjustment if deemed necessary. RYGB clearly reduces the bioavailability of metoprolol from a CR tablet. After RYGB clinicians may consider to increase the dose according to clinical response.

CLINICAL IMPLICATIONS

There is a paucity of information on the use of medication after bariatric surgery. With this thesis we just explored some aspects of optimal pharmacotherapy after bariatric surgery.

The following implications for clinical practice may be derived from the results of our research.

- Data from a very large UK primary health care database show that bariatric surgery increases the chance of remission of T2DM. Gastric bypass and sleeve gastrectomy show higher remission rates compared with gastric banding. The largest decreases in HbA_{1c} and blood glucose levels were observed in the first 2 years after bariatric surgery. Although the risks and possible adverse effects of surgery should be weighed against its benefits, bariatric surgery and, in particular, gastric bypass or sleeve gastrectomy may be considered a realistic treatment option for T2DM in patients with a BMI of 35 or greater.

- In spite of guidelines to avoid NSAIDs after surgery, their use by bariatric surgery patients is considerable. Moreover, many NSAID users do not use a PPI. Informing patients and their general practitioners by letter, in addition to care-as usual, is not an effective intervention to reduce the use of NSAIDs after bariatric surgery. The most effective way to lower the use of NSAIDs after bariatric surgery, and to promote simultaneous use of a PPI if an NSAID is still necessary, has yet to be determined.

- RYGB may influence the bioavailability of metoprolol from IR tablets. After intake of an IR tablet of metoprolol exposure of metoprolol may be reduced or increased. The consequences of RYGB for dosing metoprolol IR tablets cannot be predicted for the individual patient. Therefore, in daily clinical practice, patients using metoprolol IR tablets should be closely monitored after RYGB. If necessary, the dosage of metoprolol should be adjusted. RYGB reduces the bioavailability of metoprolol from a CR tablet. After RYGB the dose of metoprolol CR tablets should be increased, according to clinical response. For patients using metoprolol after RYGB, close monitoring and an individualized approach for adjusting metoprolol therapy are necessary.

To be able to perform medication surveillance and for optimal patient counseling, pharmacists should identify the patients who underwent bariatric surgery and register the type of surgery. Knowledge of bariatric surgical procedures and their possible influence on the use and bioavailability of medications, is an important condition of optimal medication surveillance.

FUTURE PERSPECTIVES

In **chapter 2**, we reported the results of a literature review on the influence of bariatric surgery on the use and pharmacokinetics of some frequently used drugs. We concluded that some studies have been published on medication use before and after bariatric surgery, showing a reduction in medication use for comorbidities such as diabetes, hypertension, and hyperlipidemia. However, studies assessing the change in the use of medication, did not consider changes in dosage or dosage form, which might have been implemented because of adverse drug events or an inadequate therapeutic effect. We also found, that literature on the influence of bariatric surgery on the pharmacokinetics of some frequently used drugs is sparse. Most of the available data concerned RYGB or other predominantly malabsorptive procedures. Although the RYGB is still the most performed surgical procedure worldwide, its use has declined and predominantly restrictive procedures such as sleeve gastrectomy have rapidly increased in popularity [2]. To establish the effects of these types of bariatric surgery on pharmacokinetics more studies are needed.

In our observational study on the influence of bariatric surgery on the use of medication in patients before and after surgery (**chapter 3**) dispensing data provided detailed information on type of drug, number of medications and daily dosage. Nonetheless, in this study no information on the reasons for discontinuation or for dosage change of medication was collected. Patients were not questioned about the actual use of medications and involvement with their medication.

It is thought that for chronic illnesses approximately 50% of patients do not take their medications as prescribed [4]. A NICE guideline covering medication adherence provides recommendations on the process of involving patients in decisions about medications and on supporting the patient in their adherence to medication [5]. The principles of this guideline also apply to patients using medication after bariatric surgery. Future research on changes in pharmacotherapy caused by improvement or resolution of comorbidities, as well as altered pharmacokinetics of drugs after bariatric surgery, should also involve patient perspectives. What do patients experience when using medication after bariatric surgery, while comorbidities improve or resolve? Do they report more side effects, or a lower efficacy of their medications to their physicians because of altered pharmacokinetics? Do patients have difficulties in taking medications after bariatric surgery? These and other questions have to be answered for detailed study of the effects of bariatric surgery on the use of medication.

In **chapter 4** we established a relation between health outcome and change in use of medication after bariatric surgery. In a retrospective cohort study in patients with T2DM we assessed the effect of different types of bariatric surgery on diabetes remission compared with matched control patients, and the effect on improvement of glycemic

control and related clinical parameters. Gastric bypass and sleeve gastrectomy showed higher remission rates compared with gastric banding. The results of our study are comparable with those of a systematic review and meta-analysis of randomized clinical trials on bariatric surgery vs nonsurgical treatment for obesity by Gloy et al [6]. They found that after bariatric surgery, patients had a higher remission rate of T2DM compared with nonsurgical treatment. However, different definitions for T2DM remission were used. We used strict criteria for the definition of remission of T2DM. Nonetheless, in our study the mean follow-up after bariatric surgery was 2.4 years. To determine whether the clinical effectiveness of bariatric surgery in diabetes outcome, including adverse effects and safety, is lasting, long term follow-up studies are needed. As results from population-based studies may better reflect daily practice than results from randomized clinical trials, data from primary health care may then be extremely valuable.

Clinical practice guidelines recommend avoidance of NSAIDs after bariatric surgery, because they have been implicated in the development of anastomotic ulcerations and perforations [7]. Nonetheless, in our observational study on changes in the use of medications by patients after bariatric surgery, we found that a substantial part of the patients used an NSAID at any moment after surgery (**chapter 3**). To optimize pharmacotherapy after bariatric surgery, we set up a randomized controlled intervention study to determine the effect of an, compared to care-as usual, additional intervention to reduce use of NSAIDs in patients after bariatric surgery, and to determine the use of a PPI in patients who use NSAIDs (**chapter 5**). However, the intervention, consisting of informing patients and their general practitioners by letter, was not effective. To decrease the use of NSAIDs after bariatric surgery, community pharmacists might have an active role, as pharmacist-led interventions have demonstrated to improve safe use of nonselective NSAIDs in patients at increased risk of gastrointestinal side effects [8].

To be able to perform optimal medication surveillance, pharmacists should know the patients who underwent bariatric surgery and register the type of surgery. Nonetheless, comprehensive medication surveillance may be hampered by over the counter use of NSAIDs. As most patients in our study reported over the counter use of an NSAID without concomitant use of a PPI, safe use of over the counter NSAIDs is a dangerous illusion. In the self-reported indications for an NSAID by the patients in this study, joint disorders were frequently mentioned. For this indication, NSAIDs are difficult to substitute. This might partly explain the failure of the intervention of this study. It would be interesting to know whether joint disorders were the real indication for prescription.

In a randomized trial in patients with osteoarthritis and rheumatoid arthritis celecoxib was associated with a significantly lower risk of gastrointestinal adverse events than was diclofenac plus omeprazole [9]. In search for a safe analgesic for use after bariatric

surgery, celecoxib, a cyclo-oxygenase-2 selective NSAID, may offer an attractive alternative to a non-selective NSAID plus a PPI.

For NSAIDs further exploration of optimal pharmacotherapy after bariatric surgery is necessary. Future studies could focus on determination of the optimal strategy to reduce use of NSAIDs or, if use is still necessary, promoting concurrent use of a PPI. Medication surveillance by pharmacists may be critical to that. Clarifying indications for prescribing NSAIDs in bariatric surgery patients may be another subject for future research.

The pharmacokinetic study on metoprolol was performed 6 months after RYGB. However, RYGB is a surgical procedure with lifelong consequences. Repeating this study 2 or 5 years post-surgery when weight loss is stabilized and intestinal adaptation may have occurred, will give additional information on the long-term influence of RYGB on the bioavailability of metoprolol. As other bariatric procedures, such as gastric sleeve, become more popular, the influence of these procedures on the bioavailability of orally administered medication should be addressed in future pharmacokinetic studies.

After bariatric surgery changes in drug disposition may be multicausal, not only due to changes in the anatomy of the gastrointestinal tract and physiology, but also to subsequent weight loss [11]. Darwich et al. showed that analysis of pharmacokinetic parameters such as solubility, permeability in the gastrointestinal tract, and main route of elimination is not adequate enough to explain observed trends in altered oral drug bioavailability following bariatric surgery, although solubility may potentially play an important role [12].

Specific characteristics of drugs such as, molecular size, charge, pKa, lipid solubility, enteric and hepatic metabolism, renal excretion and specific properties of the oral drug formulation (liquid solution, suspension, immediate release solid dosage form, enteric coated, extended release) must also be considered as possibly affecting the bioavailability of a drug, and thereby efficacy and adverse effects after bariatric surgery. The GISS might be useful to study the dissolution of controlled release formulations of drugs, or the dissolution of drugs with known bioavailability problems, frequently used by patients before and after RYGB.

Although use of pharmacokinetic models may be helpful to characterize the influence of bariatric surgery on drug disposition in more detail, predicting specific changes and the magnitude of changes after surgery is a major challenge [13-16]. Moreover, observed changes in pharmacokinetics of a drug after RYGB may not be of clinical importance [11].

CONCLUSIONS

This thesis explored pharmacotherapy after bariatric surgery. After bariatric surgery, in particular after restrictive-malabsorptive procedures, the use of several drug classes may be significantly decreased. Population-based data confirmed the benefits of bariatric surgery, especially gastric bypass and gastric sleeve, in improving glycemic control and remission of T2DM. The best way to reduce the use of NSAIDs, or to promote concomitant use a PPI after bariatric surgery, has yet to be found.

The bioavailability of metoprolol from various tablet formulations may be influenced by RYGB. Therefore, in daily clinical practice, patients using metoprolol IR tablets should be closely monitored after RYGB. If necessary, the dosage of metoprolol should be adjusted. RYGB reduces the bioavailability of metoprolol from a CR tablet. After RYGB the dose of metoprolol CR tablets should be increased, according to clinical response.

As so little is known about the use and pharmacokinetics of medication after bariatric surgery, the exploration of optimal pharmacotherapy after bariatric surgery needs to be continued. Meanwhile, after bariatric surgery, close monitoring of patients is warranted, adjusting dosage and formulation of medications if deemed necessary.

REFERENCES

1. Colquitt JL, Picket K, Loveman E, et al. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014;8:CD003641.
2. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery worldwide 2013. Obes Surg. 2015;25:822-32.
3. Padwal R, Brocks D, Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical complications. Obes Rev. 2010;11:41-50.
4. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86:304-14.
5. Nunes V, Neilson J, O'Flynn N, et al. Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. 2009.
6. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ 2013;347:f5934.
7. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative, nutritional, metabolic, and nonsurgical support of the bariatric surgery patient – 2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Rel Dis. 2013;9:159-91.
8. Teichert M, Griens F, Buijs E, et al. Effectiveness of interventions by community pharmacists to reduce risk of gastrointestinal side effects in nonselective nonsteroidal anti-inflammatory drug users. Pharmacoepidemiol Drug Saf. 2014;23:382-9.
9. Chan FKL, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet 2010;376:173-9.
10. Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. Am J Health Syst Pharm. 2006;63:1852-57.
11. Greenblatt HK, Greenblatt DJ. Altered drug disposition following bariatric surgery: a research challenge. Clin Pharmacokinet. 2015;54:573-9.
12. Darwich AS, Henderson K, Burgin A, et al. Trends in oral drug bioavailability following bariatric surgery: examining the variable extent of impact on exposure of different drug classes. Br J Clin Pharmacol. 2012;74:774-87.
13. Darwich AS, Pade D, Ammori BJ, et al. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol. 2012;64:1008-24.
14. Darwich AS, Pade, Rowland-Yeo K, et al. Evaluation of an *in silico* PBPK post-bariatric surgery model through simulating oral drug bioavailability of atorvastatin and cyclosporine. CPT Pharmacometrics Syst Pharmacol. 2013;2:e47.
15. Brill MJE, Välitalo PAJ, Darwich AS, et al. A semi-physiologically based pharmacokinetic model for midazolam and CYP3A mediated metabolite 1-OH-midazolam in morbidly obese and weight loss surgery patients. CPT Pharmacometrics Syst Pharmacol. 2016; 5: 20–30.
16. Gesquiere I, Hens B, van der Schueren B, et al. Drug disposition before and after gastric bypass: fenofibrate and posaconazole. Br J Clin Pharmacol. 2016;82:1325-32.