CHAPTER 2

INFLUENCE OF BARIATRIC SURGERY ON THE USE AND PHARMACOKINETICS OF SOME MAJOR DRUG CLASSES
ABSTRACT

The purpose of this review is to evaluate the influence of bariatric surgery on the use and pharmacokinetics of some frequently used drugs. A PubMed literature search was conducted. Literature was included on 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. Therefore, more clinical studies are needed on the influence of bariatric surgery on the pharmacokinetics of major drugs.
INTRODUCTION

Worldwide obesity is a growing problem. In 2008 an estimated 205 million men and 297 million women had a body mass index (BMI) of 30 kg/m² or higher [1]. Bariatric surgery is the only treatment for morbid obesity (BMI > 40) that has been shown to produce long term weight loss [2]. Several metabolic surgical techniques are available including purely restrictive (gastric banding) and restrictive/malabsorptive (gastric bypass) procedures. Of these techniques, the Roux-en-Y gastric bypass is the most commonly performed procedure [3]. Morbid obesity is associated with many comorbidities and reduced life expectancy [2]. Patients undergoing bariatric surgery have excess weight accompanied by multidrug use for multiple medical comorbidities. Bariatric surgery can influence the prevalence and incidence of comorbidities as well as the pharmacokinetics of drugs. For accomplishing optimal effects in patients, this might lead to changes in pharmacotherapy. After bariatric surgery, the use of a drug may be continued or stopped, and the dosage or dosage form may be changed because of adverse drug events or to achieve an optimal therapeutic effect. Different surgical procedures may each have specific effects on factors influencing absorption, like drug disintegration and dissolution, mucosal exposure, and absorption across the intestine, and therefore the pharmacokinetics of a drug may be changed after bariatric surgery [4]. After procedures involving gastric restriction, drug disintegration and dissolution may be altered by changes in gastric mixing, pH, and gastric emptying. This may affect the absorption of oral solid formulations like coated or controlled release preparations [4]. In diversionary and malabsorptive procedures, absorption may be reduced because of slow dissolution properties of the drug. Absorption of lipophilic drugs may be affected by less bile salt solubilization and enterohepatic recirculation [4]. Because bypass procedures reduce functional gastrointestinal length, drug absorption may be reduced; however “intestinal adaptation”, mucosal hypertrophy within the remaining intestine resulting in an increase of absorptive capacity, might counterbalance this [4]. Although bariatric surgery may theoretically have effects on the pharmacokinetics of drugs, surprisingly few clinical data are available.

Reviews so far focused on drug distribution in obesity and after bariatric surgery [5,6] and medication and nutrient administration considerations after bariatric surgery [7]. Padwal et al. reviewed the literature by examining the effects of bariatric surgery on drug absorption in relation to type of procedure [4]. However, drugs used for serious obesity-associated conditions, like major depression and cardiovascular and endocrine diseases in patients undergoing bariatric surgery, have not been the primary focus yet. For optimal drug use in these conditions, a clear understanding of the influence of bariatric surgery on the pharmacokinetics is necessary. Therefore, we studied the available literature on the influence of bariatric surgery on drug use and the pharmacokinetics of some frequently used drugs for depression, and cardiovascular and endocrine diseases.
LITERATURE REVIEW

We performed a PubMed literature search. Search terms included bariatric surgery OR malabsorptive surgery OR weight loss surgery OR gastric bypass OR metabolic surgery AND <name of drug class>. The drug classes to be searched for were antidepressants, antidiabetics, statins, antihypertensive agents, corticosteroids, oral contraceptives, and thyroid drugs. The search was limited to articles published in English from January 1990 to October 2012 and is considered up-to-date as of October 12, 2012. Related articles were also reviewed in this search. All titles and abstracts were screened for eligibility. Relevant articles were reviewed to obtain information on the influence of bariatric surgery on pharmacoepidemiology and pharmacokinetics. In Table 1, an overview of the number of relevant articles from the literature search is shown.

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PE pharmacoepidemiology; PK pharmacokinetics

Antidepressants

Bariatric surgery may have various effects on the use of antidepressants. On the subject of the use of antidepressants, Segal et al. reported a 9% decrease in the mean number of prescriptions 12 months after bariatric surgery [8]. However, in a retrospective study of 439 patients who had undergone Roux-en-Y gastric bypass, Cunningham et al. found that 23% of the patients had an increase in their antidepressant use, 40% continued to require the same antidepressant, 18% had a change in antidepressant medication, and only 16% had a decrease or discontinued their antidepressant [9]. Voelker et al. reported on the potential effects of gastric bypass surgery on the use of antidepressant medications. Tricyclic antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are highly lipophilic antidepressant drugs, well absorbed in the normal gastrointestinal tract. After gastric bypass surgery, the volume of distribution might be lower because of less adipose tissue. The concentration of drug-binding α-1-acid glycoprotein (AAG) has been reported to double in obese patients.
In weightloss after surgery, serum AAG may decrease, possibly requiring dose adjustments for highly bound drugs like TCAs [10].

In an in-vitro dissolution study, Seaman et al. demonstrated that the solubility of oral psychiatric medication preparations including amitriptyline, venlafaxine, and SSRIs like paroxetine, sertraline and citalopram may be altered after gastric bypass, but they did not reveal differences in absorption [11]. Roerig et al. performed a case-controlled pharmacokinetic study comparing the area under the curve (AUC) for a single dose of sertraline 100 mg between five subjects at 9-15 months after Roux-en-Y gastric bypass and five nonsurgical control subjects [12]. They found the AUC$_{0-10.5}$ and maximal plasma concentration to be significantly smaller in the surgery group. They conclude that the data suggest that the surgical procedure alters either the amount of drug absorbed or the time during which the absorption occurs, or both [12]. According to Hamad et al., patients taking serotonin reuptake inhibitors may have a risk for reduced bioavailability after Roux-en-Y gastric bypass surgery, so they recommend close psychiatric monitoring after surgery [13]. In 12 patients using different serotonin reuptake inhibitors (venlafaxine, citalopram, escitalopram, sertraline, duloxetine) they carried out pharmacokinetic studies 1 month before and 1, 6 and 12 months after Roux-en-Y gastric bypass. In eight patients, AUC values at 1 month after surgery had decreased in comparison to preoperative values. At 6 months after surgery, in six of these patients AUC levels had returned to baseline or greater [13].

Data from literature on the use and pharmacokinetics of antidepressants after bariatric surgery are limited. However, after bariatric surgery, clinicians should closely monitor patients on antidepressant therapy for recurrence of depressive symptoms and for side effects, adjusting dosage or formulation if necessary.

**Antidiabetics**

In literature, many articles can be found on the topic of bariatric surgery and antidiabetics. Several reviews on different aspects of bariatric surgery and its influence on type 2 diabetes concluded that surgical treatment for obese patients may be considered an additional treatment option for the management of type 2 diabetes, [14-18]. Bariatric surgery results in significant weight loss and in resolution or improvement of type 2 diabetes mellitus, as shown by cessation or reduction of oral antidiabetics and insulin. In a prospective study on the health benefits of gastric bypass surgery after 6 years, Adams et al. showed that 62 % remission of diabetes was maintained at year 6 [19]. However, details of use of antidiabetic medication are not given.

Articles in which attention is being to paid to the use of antidiabetics may be divided into studies on the effect of bariatric surgery on type 2 diabetes (retrospective studies and randomized clinical trials) and studies on the use of antidiabetic medication after bariatric surgery.
Retrospective studies have been carried out on outcome of type 2 diabetes mellitus after bariatric surgery [20-24], but in all of these studies with varying number of patients, different surgical techniques, and sometimes too short follow-up after surgery, the use of antidiabetic medication was not the primary focus.

So far, only three randomized controlled clinical trials have shown superiority of surgery over medical care for type 2 diabetes. In all trials different surgical techniques were used: gastric banding [25], Roux-en-Y gastric bypass and biliopancreatic diversion [26], and Roux-en-Y gastric bypass and sleeve gastrectomy [27]. These studies have been carried out on glycemic control parameters after bariatric surgery or on cessation or reduction of medication use for diabetes.

We found relatively few studies on the use of antidiabetic medication after bariatric surgery. They all showed a significant decrease in the use of oral antidiabetics and insulin after surgery [8, 28-31]. However, in these studies, all using different types of bariatric surgery, either the number of included patients using antidiabetics before surgery is small [29,31], or no details were provided on specific oral antidiabetic agents or dosages [8,28,30]. Several studies on the cost of medication in patients after bariatric surgery also showed a significant reduction for diabetes medication [32-38].

So far, only one study on the pharmacokinetics of antidiabetic medication is published. Metformin is the first-line drug of choice for the treatment of type 2 diabetes. Since metformin is primarily absorbed in the upper small intestine, Padwal et al. hypothesized that absorption would be significantly reduced in patients after Roux-en-Y gastric bypass. In a single-dose pharmacokinetic study in 16 non-diabetic patients after gastric bypass and 16 matched control subjects, they studied metformin absorption and bioavailability after administration of two 500 mg tablets. In patients after gastric bypass, they found an increase in metformin absorption and bioavailability in comparison with the control subjects [39]. Further studies are needed to establish whether this finding may have consequences for dosing of metformin after gastric bypass surgery.

Bariatric surgery reduces the use of antidiabetic medication. Studies published so far suffer from methodological problems or do not provide enough details with regard to drug usage. In future studies on the effect of bariatric surgery on type 2 diabetes, specific information should be gathered on the use of antidiabetics (agent, dosage, dosage form). Moreover, more interest is needed for the pharmacokinetics of oral antidiabetics.
**Statins**

Only a few studies were found on the use of medication after bariatric surgery with data on lipid-lowering agents. Segal et al. investigated the use of medication after bariatric surgery in a cohort study on 6,235 patients. They found that, at 12 months after surgery, the use of medication for dyslipidemia was reduced by 59% in non-diabetic and by 54% in diabetic patients, which may suggest a substantial resolution of dyslipidemia [8]. In a study on 298 veterans with hyperlipidemia who had undergone bariatric surgery Maciejewski et al. found that 40% had discontinued their lipid-lowering medication within 1 year after surgery [30]. Schauer et al. showed that there was a significant reduction in the number of medications needed to treat hyperlipidemia in patients after gastric bypass and sleeve gastrectomy as compared with patients on intensive medical therapy for diabetes [27].

Limited data are available on the effects of bariatric surgery on the pharmacokinetics of statins. In two different studies, Skottheim et al. found atorvastatin to be a suitable model drug for investigating the influence of the proximal intestine on drug availability. Atorvastatin shows low bioavailability when orally administered, is highly protein bound, and is a substrate for CYP3A4 and CYP3A5, as well as for the efflux transporter P-glycoprotein. In a study in 12 patients, they investigated the effect of gastric bypass on the bioavailability of atorvastatin. Gastric bypass surgery showed a variable effect on systemic exposure to atorvastatin, ranging from a 2.9-fold decrease to a 2.3-fold increase. The effect is complex but likely to depend on both available absorption area and the metabolic capacity of the bypassed small intestine [40]. In another pharmacokinetic study in ten patients after biliopancreatic diversion with duodenal switch, Skottheim et al. found increased bioavailability of atorvastatin, indicating the great influence of the bypassed highly metabolically active proximal small intestine on bioavailability [41].

Simvastatin, like atorvastatin, is a lipophilic drug; however, it is a prodrug needing hydrolysis for forming the active metabolite [42]. The influence of bariatric surgery on the first-pass metabolism of simvastatin is unknown. Pravastatin is a statin with hydrophilic properties, moderately bound to plasma proteins and not undergoing substantial metabolism by the CYP450 system [42]. Because of these properties, it may be postulated that bariatric surgery hardly affects the pharmacokinetics of this drug. Research is needed to establish whether pravastatin from a pharmacokinetic point of view may be the most appropriate statin after bariatric surgery. Bariatric surgery is effective for decreasing the use of medication for dyslipidemia. The effect of bariatric surgery on the pharmacokinetics of statins is complex; therefore, after surgery, patients on statins should be retitrated on the lowest dose possible while monitoring the plasma lipid profile.
Antihypertensive agents

In three different studies on the costs of medication in obese individuals undergoing bariatric surgery, significant savings for cardiovascular or hypertensive medication were shown, implying decrease in use of medication [32,33,37].

In a study on 42 patients with excess weight following Roux-en-Y gastric bypass surgery Donadelli et al. found that all indicators of cardiac risk improved significantly after gastric bypass, except for systolic and diastolic blood pressure, with 43 % of the patients taking antihypertensive medication before surgery and 17 % continuing antihypertensive treatment 2 years after surgery [43]. In a study on medication use after bariatric surgery, the use of cardiac medication decreased by 54 % and the use of diuretics decreased by 51 % in the postoperative period [44]. Segal et al. reported a 51 % decline in the use of medication for hypertension at 12 months after bariatric surgery [8]. In their study on bariatric surgery versus intensive medical therapy in obese patients with diabetes, Schauer et al. also showed that there was a significant reduction in the use of antihypertensive agents in patients after gastric bypass and sleeve gastrectomy as compared with patients on intensive medical therapy for diabetes [27]. In a study on the impact of bariatric surgery on comorbidities and medication use, a significant decrease for total cardiovascular disorders from 43.6 % before the operation to 14.2 % after 3 years was observed. The use of cardiovascular medication dropped from 43.7 % presurgery to 25.5 % 3 years postsurgery [45]. For antihypertensive treatment diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers are frequently used. In literature, only studies on pharmacokinetics of beta blockers were found.

Wójcicki et al. investigated the pharmacokinetics of propranolol and atenolol in patients after partial gastric resection [46]. The study was carried out in 29 patients after gastric resection with Billroth I anastomosis and in 18 healthy volunteers as controls. Pharmacokinetics of propranolol and atenolol was studied after a single oral dose of 80 mg and 100 mg, respectively. The pharmacokinetic parameters of propranolol after partial gastrectomy were significantly different from those in the control subjects: a decrease in AUC by 32 % and a decrease in C\text{max} by 20 % were noted. However, the pharmacokinetic parameters of atenolol in patients after partial gastrectomy did not reveal any significant differences compared with the controls [46]. Although propranolol and atenolol are both basic agents, they have different solubilities as propranolol is a lipophilic drug and atenolol is a hydrophilic compound. Following partial gastrectomy, the most important parameter alterations are decreased acidity and gastric secretion, and accelerated motility. An increase in pH of gastric secretion promotes the absorption of weakly basic drugs, including propranolol and atenolol [47]. However, an increase of pH will decrease the solubility of basic drugs in the stomach, contributing to a reduction in the rate of absorption in the small intestine. The lipophilicity of propranolol may be responsible for the observed impairment of drug absorption in patients after partial gastrectomy.
After bariatric surgery, the use of antihypertensive agents is reduced. If beta blocker therapy after bariatric surgery is still necessary, a hydrophilic compound like atenolol may be preferred.

**Corticosteroids**
Several studies were performed to investigate the effects of bariatric surgery on the use of respiratory medication and oral and inhaled corticosteroids. All of these studies showed a decrease in the use of antiasthmatic drugs [44,45,48,49]. In patients treated with laparoscopic adjustable banding, which is associated with less weight loss, reduction in the use of medication was less.

Research on the use of oral corticosteroids after bariatric surgery is limited. There are no studies on the absorption or pharmacokinetics of corticosteroids after bariatric surgery.

**Oral contraceptives**
Merhi provided an overview of reproductive physiology after bariatric surgery [50]. He concluded that bariatric surgery seems to improve fertility status, sexuality, pregnancy outcomes, and reproductive hormone profile, but bariatric surgery is possibly linked to contraceptive failure with the use of oral contraceptives. The use of oral contraceptives might not be trusted, most likely because of malabsorption entailed by bypassing part of the gastrointestinal system and postoperative complications like diarrhea and vomiting [50]. In a prospective study in 40 women who underwent biliopancreatic diversion (BPD), Gerrits et al. evaluated the hormone status preoperatively and postoperatively. Fertility increased after BPD. From the nine patients using oral contraceptives, two patients developed an unforeseen pregnancy in the postoperative period despite the use of the same oral contraceptive before and after BPD [51]. According to Merhi, the effect of oral contraceptives after weight loss by malabsorptive bariatric surgery is understudied. Prescribing oral contraceptives needs to be done with caution. To minimize the side effects of oral contraceptives increasingly lower hormone dosages are used. Attention is needed for the postoperative period of surgical weight loss that may further reduce the bioavailability of oral contraceptives and thus compromise contraceptive protection. Other methods of contraception might be safer [52]. In a systematic review of the literature, Paulen et al. also concluded that evidence regarding the effectiveness of oral contraceptives in women with a history of bariatric surgery is quite limited [53].

In literature, data on the safe and effective use of oral contraceptives after bariatric surgery are very limited. Clinicians should be aware of possible drawbacks of using oral contraceptives. Alternative methods of contraception might be considered.
**Thyroid drugs**

In a cohort study on 6,235 patients with bariatric surgery, Segal et al. found that the probability of thyroid replacement medication use per person at surgery was 0.17. With regard to medication use, they showed that in a time period from before bariatric surgery up to 12 months afterwards the medication use per person for thyroid replacement medication remained relatively constant [8]. Different results for the use of thyroxine medication after bariatric surgery were found in two studies with a small number of patients. In a retrospective study of patients who underwent laparoscopic Roux-en-Y gastric bypass, 23 of 224 (10.3 %) patients were treated for hypothyroidism pre-operatively. After surgery, hypothyroidism improved and thyroxine requirements were reduced in ten of 23 (43.5 %) patients [54]. In a retrospective review of 20 morbidly female patients with hypothyroidism who underwent laparoscopic Roux-en-Y gastric bypass surgery, Fazylov et al. found that based on the use of thyroid medication hypothyroidism improved or remained unchanged in most patients except for those whose thyroid disease was autoimmune in nature [55]. However, Gniuli et al. studied thyroid function in 45 patients before and after biliopancreatic diversion and concluded that the surgery increased the prevalence of subclinical or even frank hypothyroidism. Before surgery, 23 % of the subjects had subclinical hypothyroidism; at 2 years after surgery, 40.4 % of the study population had subclinical hypothyroidism. After surgery, TSH levels were increased, while free triiodothyroxine (fT3) and iodine excretion with urine decreased significantly. Levothyroxine supplementation was increased in all previous subclinical hypothyroid subjects and was started in newly onset subjects. Low circulating levels of fT3 may be a consequence of inadequate levothyroxine replacement due to altered gut absorption. However, fT3 decrease could also be caused by the surgically induced anatomical modifications of the gastrointestinal tract interfering with the enterohepatic axis. Free T3 is mainly produced in the liver by T4 de-iodination, excreted with the bile, and reabsorbed through the enterohepatic circulation. After biliopancreatic diversion, the enterohepatic circulation is an open loop, resulting in fecal loss of fT3 [56].

Rubio et al. showed that levothyroxine absorption was not decreased after Roux-en-Y gastric bypass surgery [57]. They conducted a pharmacokinetic study in two groups of 15 patients each, just before or 2-3 months after surgery, administering a single oral dose of 600 µg of levothyroxine. The subjects did not act as their own control. They found that increases in total T4 and free T4 were higher in the surgical group in comparison to the non-surgical group. However, there was a significant delay in the absorption of levothyroxine in patients who had undergone surgery [57].

Obese patients scheduled for bariatric surgery should be screened for thyroid dysfunction and, if replacement therapy is necessary, strictly monitored.
CONCLUSION

The number of patients undergoing bariatric surgery is rapidly increasing. Some studies on medication use before and after bariatric surgery showing a reduction in medication use for comorbidities like diabetes, hypertension, and hyperlipidemia have been published [8, 44,45], but studies assessing the change in the use of medication before and after bariatric surgery did not consider changes in dosage or dosage form, which might have been implemented because of adverse drug events or an inadequate therapeutic effect.

Literature on the influence of bariatric surgery on the pharmacokinetics of frequently used drugs is sparse. Theoretically, reduced drug absorption may occur after bariatric surgery. Medication formulations may then be critical to ensure adequate absorption [58].

At least for drugs and drug classes frequently used by patients after bariatric surgery, more clinical studies are needed on the influence of bariatric surgery on the pharmacokinetics. Clinical drug intervention studies may be performed next. Until more is known about the optimal use of drugs (dosage and dosage form) after bariatric surgery, close monitoring of the use of medication and its effects in the individual patient is necessary.
REFERENCES


