Exploring optimal pharmacotherapy after bariatric surgery: where two worlds meet

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER GENERAL INTRODUCTION
OBESITY

Worldwide overweight and obesity are a growing problem and prevalence rates are increasing. In 2014, more than 1.9 billion adults were overweight. Of these over 600 million adults were obese. Except for parts in sub-Saharan Africa and Asia globally there are more people who are obese, than underweight [1]. As index to classify overweight and obesity the body mass index (BMI) is used. The BMI is a person’s weight in kilograms divided by his height in metres (kg/m²). The World Health Organization (WHO) classification of the BMI is shown in Table 1. In 2015 half of the Dutch aged 20 years and older were overweight (BMI ≥ 25), more men than women (54.4% versus 46.3%). However, more women than men were obese. In total 13.7% of the Dutch were obese (BMI ≥ 30) [2]. Overweight and obesity are associated with increased risk of a wide range of chronic diseases, such as cardiovascular diseases, type 2 diabetes mellitus, several types of cancer, musculoskeletal disorders (especially osteoarthritis), as well as a reduced life expectancy [1,3]. Strategies to prevent the rising prevalence of obesity have had little effect so far. The cornerstone for treatment of a patient with obesity is a combination of lifestyle or behavioural training, dietary change to reduce energy intake, and an increase in physical activity [4]. However, the success of this approach for sustained weight loss is limited.

As long-term results are lacking, there is no place for pharmacological treatment of obesity. Moreover, in the past several drugs for treating obesity have been withdrawn from the market, because of safety concerns. Currently available drugs such as orlistat, naltrexone-bupropion and liraglutide show a modest weight loss after 1 year of therapy. Nevertheless, for these drugs the balance between efficacy and safety is negative [5-6].

TABLE 1. WHO BMI classification [1].

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity Class I (obesity)</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity Class II (severe obesity)</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Obesity Class III (morbid obesity)</td>
<td>≥ 40.0</td>
</tr>
</tbody>
</table>
**BARIATRIC SURGERY**

For morbid obesity (BMI ≥ 40) bariatric surgery is considered the most effective treatment option. Compared with non-surgical options bariatric surgery results in greater improvement in weight loss and weight associated comorbidities [7]. Five years after surgery BMI loss is in the range of 12 to 17 kg/m² [8]. Current US and European guidelines recommend to consider bariatric surgery for patients who failed to lose weight despite non-surgical treatment, if they have a BMI ≥ 40, or ≥ 35 with one or more obesity-related comorbidities, including cardio-respiratory disease, type 2 diabetes mellitus, severe joint disease, severe psychological problems, etc. [9-10]. Women are more inclined to undergo bariatric surgery than men. Almost 80% of all weight-loss surgery patients are female [8]. In 2013 worldwide nearly half a million bariatric procedures were performed, almost all laparoscopically [11]. In the Netherlands there is a large increase in the number of performed weight-loss surgeries to almost 10,000 in 2015 [12].

For bariatric surgery different surgical options are available. The traditional approach of the achievement of the weight loss effect of bariatric surgery is that bariatric procedures are either restrictive, malabsorptive, or a combination of both.

The most commonly performed bariatric surgery procedures with large variations in the preferred procedure between countries, are:

1. **Adjustable gastric band (Figure 1)**

   In this restrictive procedure an inflatable band is placed around the upper part of the stomach to create a smaller stomach pouch. The band is connected to a subcutaneous port. By using normal saline as a filling solution the diameter of the band can be increased or decreased. The intake of food is limited, creating an earlier sense of satiety [13-14]. This operation is reversible. In the Netherlands this procedure is hardly performed anymore. The rate of reoperation is high and weight loss is substantially less than with other procedures [8].

2. **Gastric sleeve (Figure 2)**

   In this procedure the greater part of the stomach is removed, leaving a thin vertical sleeve or tube with a volume of 100-150 mL. The vertical sleeve gastrectomy is a restrictive procedure. Often this gastric sleeve operation is followed by another operation. For people who are either extremely obese or have health problems that make them ineligible for gastric bypass surgery, the gastric sleeve procedure is an option to help them start losing weight. After a few years, most patients lose enough weight for another bypass procedure, the duodenal switch procedure, for further weight loss [13-14].
3. **Roux-en-Y gastric bypass (RYGB; Figure 3)**

This restrictive-malabsorptive procedure reduces the size of the stomach to a small pouch with a volume of 30-60 mL. This pouch is attached to the jejunum, bypassing most of the rest of the stomach, the duodenum and the proximal jejunum. The biliopancreatic limb is reconnected via a jejunoojejunal anastomosis to facilitate the passage of bile salts and pancreatic enzymes. RYGB achieves weight loss by combining restriction of food intake with malabsorption [13-14].

The field of bariatric surgery is continuously evolving with global and regional trends. RYGB is still the most performed bariatric procedure, but global trends show a decrease in the number of RYGB. Although long-term proof of the efficacy of the gastric sleeve is limited, the number of performed gastric sleeve procedures is rising. The gastric sleeve is the most frequently performed procedure in the USA, Canada and in the Asia-Pacific region. Other procedures, such as the omega loop gastric bypass or single anastomosis gastric bypass, have recently become more popular [11,15].
Although restriction of food intake and malabsorption are of significant importance after a bariatric procedure, the exact mechanism involved in weight loss is not yet clear. The changes in gut hormones, such as ghrelin, leptine, PYY, and GLP-1, may play an important role in appetite suppression and increased satiety in patients after bariatric surgery [16-17].

More than 20% of the patients with morbid obesity have had type 2 diabetes mellitus [18]. Bariatric surgery effectively prevents and treats type 2 diabetes mellitus [19]. Surgical treatment for obese patients may be considered an additional treatment option for the management of type 2 diabetes mellitus [20]. Thus, bariatric surgery is actually more than mere weight loss surgery. Not only anatomical, but also physiological changes may be important for the efficacy of bariatric surgery [17,21]. Therefore, for surgical procedures to treat metabolic diseases, especially type 2 diabetes mellitus, the term metabolic surgery is used [21].

Bariatric surgery is not without risks. Complications, such as anastomotic leakage, ulceration, bleeding, stomal stenosis, vomiting, and reflux may occur. Reoperation may then be necessary. Complications associated with bariatric surgery range from

**FIGURE 2.** Gastric sleeve (reprinted with permission from E.O. Aarts and adapted from [13]).
10% to 17% and reoperation rates approximately 7%. However, mortality associated with bariatric surgery is low (0.08-0.35%) [8]. After RYGB, following meals, patients may suffer from palpitations, lightheadedness, and fatigue. These are symptoms of the dumping syndrome. Early dumping begins within 30 min following a meal and is attributable to bowel distention, gastrointestinal hormone hypersecretion and autonomic dysregulation. Late dumping syndrome occurs 1-3 h postprandially with symptoms of hypoglycemia, perspiration, faintness, and decreased concentration [22]. The dumping syndrome is best prevented by dietary changes. Dietary recommendations include smaller and more frequent meals, separating eating and drinking, and decreasing carbohydrate intake [22].

Morbid obesity has been shown to be associated with a high prevalence of micronutrient deficiency, among others, due to eating behaviour and lifestyle. After bariatric surgery vitamin and mineral deficiencies, including deficiencies of vitamin A, B₃, B₁₂, D, folic acid, calcium and iron are common, especially after malabsorptive and restrictive-malabsorptive procedures. Postoperatively patients should take life-long daily nutritional supplementation [23].
MEDICATION USE AFTER BARIATRIC SURGERY

Patients undergoing bariatric surgery have excess weight accompanied by multidrug use for multiple medical comorbidities. Bariatric surgery significantly ameliorates obesity-related comorbidities, such as type 2 diabetes mellitus, hypertension, angina pectoris, myocardial infarction, dyslipidemia, and sleep apnea [8,24]. 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. Specific drug characteristics such as the mechanism of drug absorption (passive diffusion versus uptake or efflux transport), the molecular size, charge, acid-base status, pK_a, lipid solubility, and the particular mechanism of drug clearance (enteric metabolism, hepatic metabolism and renal excretion) should each be considered when studying pharmacokinetics after bariatric surgery [25-27]. Different surgical procedures may each have specific effects on factors influencing absorption, such as disintegration and dissolution, mucosal exposure, and absorption across the intestine, and therefore the pharmacokinetics of a drug may be changed after bariatric surgery [25]. Moreover, after bariatric surgery the effect on pharmacokinetics may vary in time. Table 2 shows the changes after gastric sleeve or RYGB, that may possibly affect the pharmacokinetics of an orally administered drug. 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 [25]. All things considered, a variety of factors may affect the use and pharmacokinetics of drugs after bariatric surgery.

TABLE 2. Changes after gastric sleeve or RYGB possibly influencing the pharmacokinetics of an orally administered drug [25-26].

<table>
<thead>
<tr>
<th>Change</th>
<th>Gastric sleeve</th>
<th>RYGB</th>
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<tbody>
<tr>
<td>Smaller volume of distribution</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Increased gastric pH</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduced gastric mixing</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduced exposure to digestive enzymes</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>accelerated</td>
<td>delayed</td>
</tr>
<tr>
<td>Reduced surface area for absorption</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Reduced exposure to metabolizing enzymes and drugtrans-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>porters in the intestinal wall</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Reduced exposure to bile acids and altered enterohepatic recycling</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Shorter intestinal transit time</td>
<td></td>
<td>√</td>
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</table>
AIM AND OUTLINE OF THIS THESIS

The aim of the present thesis is to explore optimal pharmacotherapy after bariatric surgery. By combining knowledge of bariatric surgical procedures and its effects on anatomy and physiology, with pharmacepidemiology and pharmacokinetics, optimal pharmacotherapy after bariatric surgery may be pursued.

To establish what is already known on this subject, in chapter 2, in the second section of this thesis on (pharmaco)epidemiology, we present a review to evaluate the influence of bariatric surgery on the use and pharmacokinetics of some frequently used drugs. We conducted a literature search, including literature on the influence of bariatric surgery on pharmacepidemiology and pharmacokinetics.

Next, the results of two (pharmaco)epidemiological studies are presented. In chapter 3, we performed a combined retrospective and prospective observational 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. Dispensing data from pharmacies of patients undergoing their first bariatric surgery was analyzed from 1 month before until 12 months after surgery. The objective of chapter 4 was to assess the effect of different types of bariatric surgery in patients with type 2 diabetes mellitus 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. This retrospective cohort study was conducted within 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.

The third section of this thesis contains the results of a study to optimize pharmacotherapy after bariatric surgery. In chapter 5, we performed a randomized controlled intervention study to determine the effect of an, compared to care-as-usual, additional intervention to reduce nonsteroidal anti-inflammatory drug (NSAID) use in patients who underwent bariatric surgery, and to determine the use of proton pump inhibitors in patients who use NSAIDs after bariatric surgery.

The next section focuses on bioavailability of metoprolol. In chapter 6 the development of a biorelevant gastrointestinal simulation system (GISS), mimicking conditions before and after Roux-en-Y gastric bypass (RYGB), for in vitro evaluation of the pharmaceutical availability of drugs frequently used by patients after RYGB, is described. Release profiles of metoprolol from metoprolol tartrate immediate release tablets and various metoprolol controlled-release tablets were determined. The objective of chapter 7 was to validate a simple, sensitive LC-MS method to quantify metoprolol and its metabolite α-hydroxymetoprolol in human serum for application
in pharmacokinetic studies. 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 and controlled-release tablets.

Finally, in chapter 9, we complete this thesis with a general discussion on the clinical impact of our research. The main findings in this thesis will be placed in perspective of future research.
REFERENCES

SECTION II

(PHARMACO)EPIDEMIOLOGY