Concepts and applications for evidence-based dosing in morbidly obese patients before and after weight loss surgery

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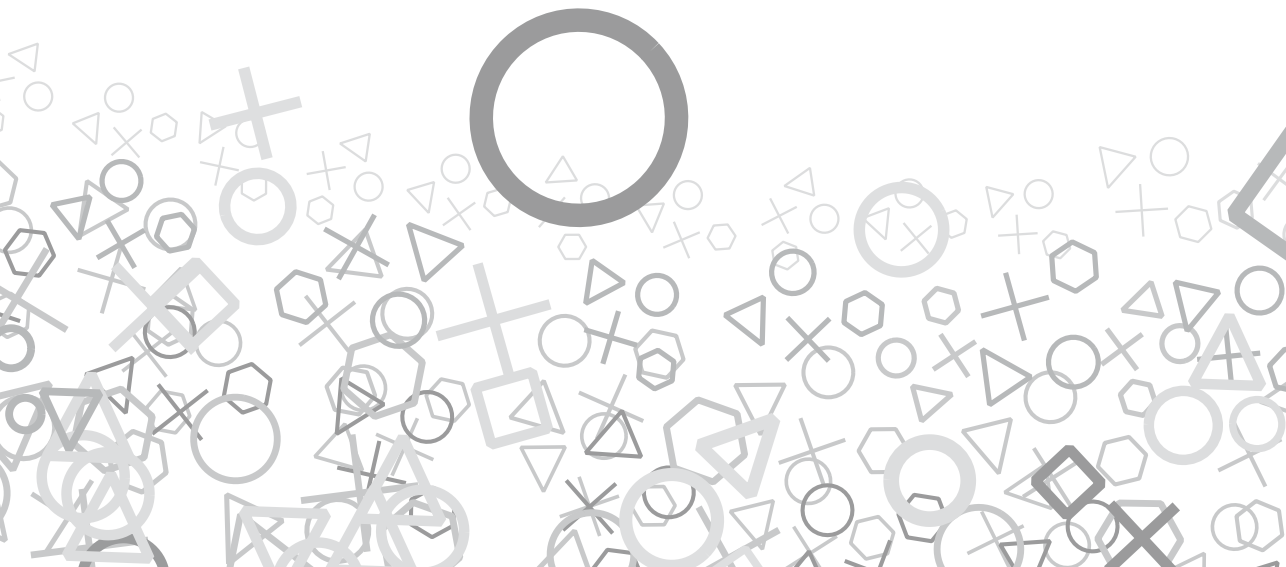
CHAPTER 1

Introduction, scope and outline of the investigations



MORBID OBESITY

The prevalence of obesity (body mass index, BMI> 30 kg/m^2) and morbid obesity (BMI> 40 kg/m^2) is increasing across the globe [1-2]. Mexico and the US seem to deal with the highest obesity prevalence rates among adults, 32% and 35% respectively [1, 3], while the estimated obesity prevalence rates for 2013 show that >50% of the women in Kuwait, Libya and Qatar are obese [4]. The average prevalence of obesity in Europe is estimated between 18-21% in 2013. In the Netherlands approximately 35% of the population is overweight (BMI>25 kg/m^2) and 13% obese [5]. Numbers of morbid obesity in Europe are lacking, but are estimated to range between 1-7% depending on the country [5-8]. A global analysis of overweight and obesity prevalence rates suggests that in developed countries the increasing obesity trend has attenuated over the past 8 years, while in the developing world the trend seems to continue to increase [4].

With obesity and morbid obesity, physiologic parameters may alter. These patients are reported to have a lower percentage of fat free mass and water relative to their total body weight [9-10], while absolute values of cardiac output and blood volume are increased in comparison to non-obese subjects [11]. Concerning liver function, non-alcoholic steatohepatitis is highly associated with morbid obesity patients and histological liver abnormalities such as fatty infiltration are present in approximately 90% of the livers of this population [12-13]. Furthermore, liver perfusion may be altered due to a combination of ballooning of hepatocytes (due to fatty infiltration) and narrowing of the peripheral hepatic micro vessels, the sinusoids [14]. For renal function, it seems that in obese subjects creatinine clearance increases with fat free mass [15] and glomerular filtration is increased in overweight and obese subjects compared to non-obese subjects [16-17].

In addition, it has been reported that obese patients have an increased risk to develop, among others, thrombosis [18], cardiovascular disease [19], cancer [20], and infections, including surgical site infections and other nosocomial infections as well as to develop serious complications of common infections[21]. The underlying causes of this increased risk are thought to be related to the metabolic syndrome and the increased inflammation status which are both highly prevalent among subjects with (morbid) obesity [22-24].

The physiological changes in obese and morbidly obese patients mentioned above may impact the pharmacokinetics and pharmacodynamics of drugs. Therefore evidence-based dosing guidelines in the (morbidly) obese population are needed, as this population deserves to receive effective and safe pharmacotherapy as much as any other patient group. In particular, in view of the increased risk of obese patients to serious comorbidities, evidence-based dosing is necessary. To reach this goal, knowledge on the extent into which these physiologic changes influence absorption, metabolism, distribution and elimination of drugs is essential. Ultimately also the influence of obesity on the pharmacokinetic-pharmacodynamic relationship should be evaluated.

In the past decades a substantial number of studies have aimed to evaluate how the pharmacokinetics of certain drugs change in obese patients. However, it seems that in the vast majority of these studies only overweight (BMI> 25 kg/m^2) and obese (BMI> 30 kg/m^2) subjects were included, while today morbidly obese patients (BMI> 40 kg/m^2) are not uncommon in the daily practice of physicians and pharmacists. In this respect, there is a strong need for pharmacokinetic studies after both intravenous and oral drug administration in morbidly obese patients to establish evidence-based dosing guidelines for this special population.

BARIATRIC SURGERY

Bariatric surgery or weight loss surgery is considered the most effective treatment option for morbid obesity [25-26] and results, among other factors, in long term weight loss, reduction in overall mortality and remission of type 2 diabetes [26-27]. Adult patients with a BMI> 40 kg/m^2 or with a BMI>35 kg/m^2 with a severe obesity-related co morbid condition such as hypertension, impaired glucose tolerance, diabetes mellitus, hyperlipidemia, or obstructive sleep apnea qualify for a bariatric surgery procedure [28-29]. Bariatric surgery comprises of many different types of surgery of which the Roux and – Y gastric bypass (RYGB, 47% in 2011) and sleeve gastrectomy (SG, 28% in 2011) are currently most performed worldwide, while the adjustable gastric banding procedure has not been performed much in recent years (18% in 2011) [30]. During a Roux and – Y gastric bypass the stomach is reduced to a small pouch and the duodenum and initial part of the small intestine are bypassed [31-32]. For a sleeve gastrectomy a large portion of the stomach along the greater curvature is removed resulting in a tube like structure along the smaller curvature [33]. The prevalence of bariatric surgery is increasing, with more than 340,000 bariatric surgeries performed worldwide in 2011 [30]. For the Netherlands, the media reported a significant increase in bariatric surgeries from 4,000 in 2011 to an estimate of 10,000 in 2013 [34].

Bariatric patients present physicians and pharmacists with many challenges regarding safe and effective drug therapy, as bariatric procedures may impact a drug's pharmacokinetics both due to the anatomical changes made to the gastro-intestinal tract and the induced loss in body weight. These anatomical changes may cause an increase in stomach pH, an increase in gastric emptying time, and a decrease in the surface area of absorption [31, 35], thus potentially affecting a drug's rate and extent of oral absorption. In addition to these anatomical alterations, bariatric patients may lose a substantial percentage of their body weight (a mean of 32% of total body weight 0.5-2 years after bariatric surgery [26]) which may have a major impact on the distribution and clearance of a drug [36].

While case reports have reported a decrease in oral drug exposure of certain drug in patients after bariatric surgery (e.g tamoxifen [37], phenytoin [38], imatinib [39]), sofar only 17 clinical studies have aimed to evaluate how a bariatric procedure alters the pharmacokinetics of approximately 25 drugs [31, 36, 40]. The results of this limited number of studies show a large variation. For some drugs, mean oral absorption remains unchanged after a gastric bypass as measured by the oral AUC (e.g. atorvastatin [41], furosemide and omeprazole [42]), while others, including erythromycine [43], tacrolimus and sirolimus [44] and tolbutamide [42], showed a substantial reduction in AUC after an oral dose. In contrast, for metformin an increase in oral AUC was reported in 16 patients after RYGB [45]. In summary, there seems to be a large variation in how bariatric surgery influences drug exposure after oral administration [36], whereas it seems that this variation cannot be related to the Biopharmaceutics Classification System (BCS) [46]. Alternatively, the impact of bariatric surgery on the absorption of a specific drug may be predicted based on the type of surgery and knowledge of the involved absorption processes of the drug (e.g. availability of transporters, bile salts, main oral absorption site, CYP3A substrate, etc.). However, due to the small number of studies, the limited number of patients included, the large variation in compounds studied and types of bariatric surgery included in these studies, no such conclusion can be derived yet.

Finally, information on how loss in body weight in morbidly obese patients after bariatric surgery affects the pharmacokinetics of drugs has only been studied for 8 drugs [42, 45, 47-48], while it is known that increase in body weight greatly affects clearance and particularly distribution of drugs.

THE OBJECTIVE OF THIS THESIS

There is a strong need for knowledge on safe and effective pharmacotherapy in morbidly obese patients and in addition, in patients which have undergone a bariatric procedure.

As a first step towards evidence-based dosing strategies in morbidly obese patients, **Chapter 2** presents an overview of studies on drug pharmacokinetics including both obese and non-obese subjects, sorted by metabolic or elimination pathway of the drug. This overview shows that the impact of obesity on drug metabolism and elimination seems to differ greatly between drugs and depends on the metabolic or elimination pathway primarily involved in the clearance of a drug. In addition, obesity may also impact oral absorption, oral bioavailability and the volume of distribution of drugs. **Chapter 3** provides an overview of the impact of obesity on absorption, distribution, metabolism and elimination of drugs as well as perspectives for future research into the influence of obesity on pharmacokinetics. It shows that (morbid) obesity may largely impact volume of distribution, while the magnitude and direction of change are difficult

to predict, while changes in clearance may be smaller than those on volume of distribution and may be predictable on the basis of the elimination pathway involved. Lastly, it describes that very little is known about the influence of obesity on oral absorption.

The clinical studies presented in this thesis focused on two drugs, i.e. cefazolin and midazolam. In **Chapter 4** a study is presented which aimed to evaluate the influence of morbid obesity on cefazolin pharmacokinetics and penetration into the subcutaneous tissue using clinical microdialysis techniques. Cefazolin is a first generation cephalosporin antibiotic which is widely applied for the prevention of surgical site infections during many types of surgical interventions, including bariatric surgery [49] and is eliminated completely by glomerular filtration and active tubular excretion [50]. It was studied because in morbidly obese patients there seem to be more surgical wound infections, while cefazolin plasma concentrations seem to reach adequate levels [21, 51]. It was unknown whether cefazolin reaches adequate levels at the target site, which is the subcutaneous adipose tissue around the surgical wounds, in morbidly obese patients..

Chapter 5 presents a study of midazolam population pharmacokinetics in morbidly obese patients. Midazolam was studied because it is the best Cytochrome P450 3A (CYP3A) substrate currently available and preliminary evidence indicates that absolute clearance of CYP3A substrates is lower in obese patients (Chapter 2) [52]. Midazolam is a widely applied drug for sleeping disorders, (pre)anesthesia and sedation in the Intensive Care. It is metabolized into 1-OH-midazolam by the CYP3A enzyme and is considered a model probe for the activity of CYP3A [53-54]. CYP3A is an important enzyme system that is involved in the metabolism of 25% of all clinically used drugs [55], including many drugs that are relevant for obese patients, such as statins, cardiovascular drugs, antipsychotics and oncolytic drugs [56]. A potentially reduced absolute clearance is highly relevant, because it may result in prolonged effect of the drug with increased risk of adverse events particularly upon prolonged use. As the CYP3A enzyme is located in the liver as well as in the gut wall, it determines both systemic clearance and oral drug bioavailability of CYP3A substrates including midazolam. For this reason a semi-simultaneous dosing design was applied in this study, in which patients first received an oral dose followed by an intravenous dose approximately 150 minutes later. This design allowed for both the evaluation of systemic midazolam clearance as well as midazolam oral bioavailability.

The influence of bariatric surgery on the pharmacokinetics of midazolam was studied in **Chapter 6**. In this study, eighteen patients of the morbidly obese patients who participated in the study of Chapter 5 were restudied one year post bariatric surgery using the same study design. Midazolam systemic clearance and oral bioavailability were closely studied in view of anticipated weight loss together with the anatomical changes to the gastro-intestinal tract, respectively.

To further investigate the CYP3A mediated metabolism of midazolam into 1-OH-midazolam, in **Chapter 7** we used midazolam and 1-OH-midazolam data and semi-phys-

iologically based PK modeling to quantify the influence of bariatric surgery on CYP3A activity in the gut wall and liver separately. This evaluation required a more advanced model in which also presystemic metabolism of midazolam into 1-OH-midazolam could be accounted for.

In **Chapter 8**, the outcomes of the Chapters 4-7 are summarized and interpreted. In addition, perspectives on future studies and directions for evidence-based dosing guidelines in morbidly obese and bariatric patients are provided with the latter being particularly of relevance for clinical practice. Finally, the relevance of these findings for other drugs which share the same elimination pathway are discussed.

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