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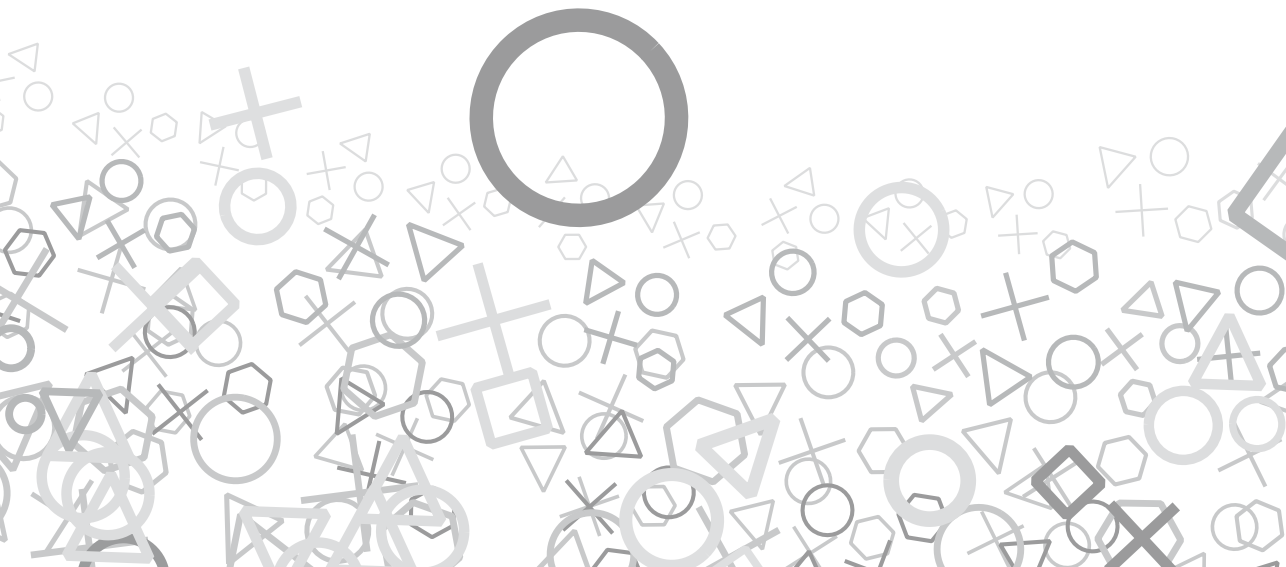
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CHAPTER 8

Concepts and applications for evidence-based dosing in morbidly obese patients before and after weight loss surgery: Summary, conclusion and perspectives



SUMMARY AND CONCLUSIONS

Introduction and background

The prevalence of morbid obesity (body mass index, BMI > 40 kg/m²) is increasing across the globe ¹⁻². The physiological changes associated with morbidly obese patients may impact the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and thus drug exposure and effects. Therefore (clinical) studies guiding evidence-based dosing in the morbidly obese population are needed, particularly in view of the increased risk of (morbidly) obese patients to develop serious comorbidities including cancer, diabetes type 2, cardiovascular diseases, etc. ³. Currently, knowledge to what extent these physiologic changes influence absorption, metabolism, distribution, elimination and ultimately efficacy and safety of drugs is largely unknown. While until today studies on drug pharmacokinetics in obesity predominantly included overweight (BMI 25-30 kg/m²) and moderately obese patients (BMI 30-40 kg/m²), there is a strong need for pharmacokinetic studies in morbidly obese patients. In the end, the influence of (morbid) obesity on the PK-PD relationship should be characterized to guide dosing in this population.

Furthermore, as a result of an increase in the number of morbidly obese patients, also the number of patients who undergo weight loss or bariatric surgery is increasing ⁴. Bariatric surgery or weight loss surgery is considered the most effective treatment option for morbid obesity ⁵⁻⁶ and results, among other factors, in long term weight loss, remission of type 2 diabetes and overall mortality ⁶⁻⁷. 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. On average, bariatric patients lose a mean of 32% of total body weight 0.5-2 years after the bariatric procedure ⁶. For these reasons, also for the bariatric patient population, insight into changes in PK and PD that can be expected and evidence-based dosing recommendations are needed.

As a first step, **Chapter 2** provides an overview of findings reported in pharmacokinetic studies in both obese and non-obese subjects which are sorted by the metabolic or elimination pathway of the drug ⁸. This overview shows that the impact of obesity on drug metabolism and elimination seems to depend on the metabolic or elimination pathway primarily involved in the clearance of a drug. It was shown that Cytochrome P450 3A (CYP3A) metabolized drugs have lower total (oral) clearance values, while clearance of drugs primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase, N-acetyltransferase or CYP2E1 appears higher in obese versus non-obese patients.

Furthermore, in **Chapter 3** an overview of the impact of obesity on each aspect of a drug's pharmacokinetics as well as perspectives for future research into the influence of obesity on pharmacokinetics are summarized⁹. This overview shows that (morbid) obesity may substantially impact the distribution of drugs, while the magnitude and direction of change are difficult to predict based on the lipophilicity of the drug alone. Relative to the influence of obesity on distribution, the impact of (morbid) obesity on clearance may be smaller and more predictable based on the elimination pathway involved (Chapter 2). Finally, Chapter 3 shows that very little is known about the influence of (morbid) obesity on oral absorption and bioavailability, while from a small number of studies it seems that oral drug absorption may be altered.

Given the lack of information on drug absorption, distribution and clearance in morbidly obese and bariatric surgery patients, we decided to study two different drugs in these populations in this thesis. First, we studied cefazolin subcutaneous tissue penetration in morbidly obese patients undergoing bariatric surgery. In addition, we evaluated the impact of both morbid obesity and bariatric surgery on the pharmacokinetics of CYP3A substrate midazolam after semi-simultaneous oral and intravenous administration.

Influence of morbid obesity on cefazolin pharmacokinetics

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 surgery¹⁰. Cefazolin is eliminated by glomerular filtration and active tubular excretion¹¹. Studies report more surgical wound infections in morbidly obese patients, while cefazolin plasma concentrations seem to reach adequate levels in morbidly obese patients¹²⁻¹³. Yet, for morbidly obese patients it was unknown whether adequate levels of cefazolin were reached at the target site, which in this case is the interstitial space fluid (ISF) of the subcutaneous adipose tissue around the surgical wounds (abdomen). Therefore, in **Chapter 4** we aimed to measure and compare unbound cefazolin concentrations in the ISF of the subcutaneous adipose tissue of morbidly obese and non-obese patients. The results were used to quantify the influence of morbid obesity on cefazolin pharmacokinetics in the subcutaneous adipose tissue taking into account protein binding of this drug¹⁴.

After a 2 gram cefazolin intravenous bolus dose, total and unbound cefazolin plasma concentrations were collected in nine morbidly obese (141 ± 22 kg, 107-175 kg) and 7 non-obese patients (86 ± 13 kg, 72-109 kg). In addition, using clinical microdialysis, unbound cefazolin ISF concentrations of the abdominal adipose tissue were collected until 4 hours after dosing. It was found that unbound cefazolin subcutaneous tissue penetration, defined by the unbound AUC ratio ($fAUC_{\text{tissue}}/fAUC_{\text{plasma}}$) was lower in morbidly obese compared with non-obese patients (0.70 (0.67-0.83) versus 1.02 (0.85-1.41), $p < 0.05$). Measured cefazolin concentrations were best described by a two-compartment

population PK model with saturable protein binding. The covariate analysis showed that central volume of distribution increased linearly with body weight and that cefazolin distribution from the central to the subcutaneous compartment decreased with body weight in a non-linear manner. Based on the final covariate population PK model, Monte Carlo simulations were performed indicating that a dose of 2 g cefazolin given prior to incision will be sufficient to prevent wound infections with pathogens for which the minimal inhibitory concentration (MIC) is 1 mg/L for a duration of 240 minutes. In contrast, the probability of target attainment for morbidly obese versus non-obese patients for MIC values of 2 and 4 mg/L is reduced (Chapter 4, Table 3 and Figure 4).

In conclusion, this study showed that cefazolin distribution to the ISF of the subcutaneous adipose tissue is reduced in morbidly obese versus non-obese patients, that cefazolin tissue distribution reduces with increasing body weight and that dose adjustments are required in this patient group (see Appendix I).

Influence of morbid obesity and weight loss surgery on the pharmacokinetics of CYP3A substrate midazolam

According to the literature review in Chapter 2 decreased CYP3A mediated clearance in obese individuals may be expected. Therefore, in **Chapter 5** we aimed to study the pharmacokinetics of midazolam in morbidly obese patients versus non-obese healthy volunteers after semi-simultaneous oral and intravenous administration¹⁵. Midazolam is a widely applied drug for short-term and long-term sedation for procedures or at the intensive care unit. It is primarily metabolized by CYP3A into 1-OH-midazolam and as such considered a probe substrate for CYP3A activity¹⁶.

In a clinical study, 20 morbidly obese patients with a mean body weight of 144 kg (range 112–186 kg) and mean body mass index 47 kg/m² (range 40–68 kg/m²) participated in the study. All patients received a midazolam 7.5 mg oral and 5 mg intravenous dose separated by 159 ± 67 minutes. In addition, data from 12 healthy volunteers were available for a population pharmacokinetic (PK) analysis using NONMEM. In the final PK model, it was found that in morbidly obese patients the population mean clearance (relative standard error %) was similar (0.36 (4%) L/min), while oral bioavailability was higher in comparison to healthy volunteers (60% (13%) versus 28% (7%), $p < 0.001$). Furthermore, we found that central and peripheral volumes of distribution increased substantially with body weight (both $p < 0.001$).

In conclusion, in morbidly obese patients, systemic plasma clearance of midazolam is unchanged, while oral bioavailability is increased. Given the large increase in volumes of distribution, dose adaptations for intravenous midazolam should be considered (see Appendix I). Further research should elucidate the exact physiological changes at intestinal and hepatic level contributing to our observations of unchanged midazolam clearance and increased oral bioavailability in morbidly obese patients.

Besides the influence of morbid obesity on the pharmacokinetics on CYP3A substrate midazolam, the influence of bariatric surgery and its associated weight loss was evaluated. For his purpose, the patients from the study in Chapter 5 were invited to participate at a second study occasion one year after the bariatric procedure. The outcomes of these investigations are reported in **Chapter 6**¹⁷.

Of the 20 morbidly obese adult patients (144 ± 22 kg) who participated in the study of Chapter 5, 18 patients participated (mean loss of 45 ± 10 kg) one year after surgery. At both study occasions, patients received 7.5 mg oral and 5 mg intravenous midazolam separated by 160 ± 48 minutes. Using population pharmacokinetic modeling, it was found that, one year after bariatric surgery, systemic clearance of midazolam was higher (0.65 (7%) versus 0.39 (11%) L/min, $p < 0.01$, respectively). This increase in clearance after bariatric surgery could not be attributed to the decrease in body weight as the body weight model was inferior to the bariatric surgery model ($p < 0.05$). In addition, mean oral transit time was faster (23 (20%) versus 51 (15%) minutes, $p < 0.01$), while oral bioavailability was unchanged (0.54 (9%)). Central and peripheral volumes of distribution were overall lower in patients one year after bariatric surgery ($p < 0.05$).

Concluding, in this cohort study in morbidly obese patients undergoing bariatric surgery, systemic clearance (CL) was 1.7 times higher one year after bariatric surgery, which may potentially result from an increase in hepatic CYP3A activity per unit of liver weight. Although oral transit time was found to be faster, oral bioavailability (F) remained unchanged, which considering the increased systemic clearance (CL) implies an increase in the fraction escaping intestinal first pass metabolism (F_G).

Based on the results of Chapter 6, it was hypothesized that the midazolam fraction escaping gut wall metabolism (F_G) is increased in patients after bariatric surgery in comparison with morbidly obese patients before bariatric surgery. Knowledge on the exact influence of a bariatric procedure on hepatic and gut wall CYP3A activity, and therefore the fraction escaping hepatic metabolism (F_H) and F_G , may be of value for many other drugs, as approximately 30% of all clinically used drugs are metabolised via CYP3A¹⁸. Therefore, in **Chapter 7** we aimed to describe the pharmacokinetics of both midazolam and its CYP3A mediated metabolite 1-OH-midazolam in morbidly obese patients before and one year after bariatric surgery after both oral and intravenous administration¹⁹. A semi-physiologically based PK (Semi-PBPK) model taking into account gut wall and hepatic first pass metabolism was required for this analysis. The results of the model were used to explore to what extent these results may affect other CYP3A substrates.

Using a semi-PBPK model, it was found that for bariatric patients midazolam intrinsic hepatic clearance ($CL_{\text{int hepatic}}$) was 1.5 times higher ($p < 0.01$) in comparison to morbidly obese patients before surgery, resulting in a decrease in F_H of midazolam in patients after bariatric surgery. In contrast, intrinsic midazolam gut wall clearance ($CL_{\text{int gut wall}}$)

showed a trend towards lower values in bariatric patients, while for both patients groups values were considered low. As a result, F_G was close to one both for patients before and after for weight loss surgery, while especially the morbidly obese patient group exhibited large inter individual variability. Simulations of increased hepatic CYP3A abundance by 1.5 times showed a plasma clearance increase of 1.30-1.41 for low extraction ratio CYP3A substrates such as cyclosporine, alprazolam and triazolam using the SimCYP simulator²⁰. For the medium extraction ratio CYP3A substrate midazolam, this resulted in only a 1.22 increase in plasma clearance.

As this factor of 1.22 is lower than the factor of 1.7 identified in Chapter 6, the results of Chapter 7, in combination with the results from Chapter 5 and 6, have been summarized in Figure 1. In this figure, plasma clearance (CL_{plasma}) values and intrinsic blood clearance values at the level of the gut wall ($CL_{\text{int gut wall}}$) and liver ($CL_{\text{int hepatic}}$) are compared to values for healthy volunteers and bariatric patients from the perspective of the morbidly obese patient. From this figure, it may be concluded that the increase in midazolam plasma clearance after a bariatric surgery is not only due to normalization of previously reduced

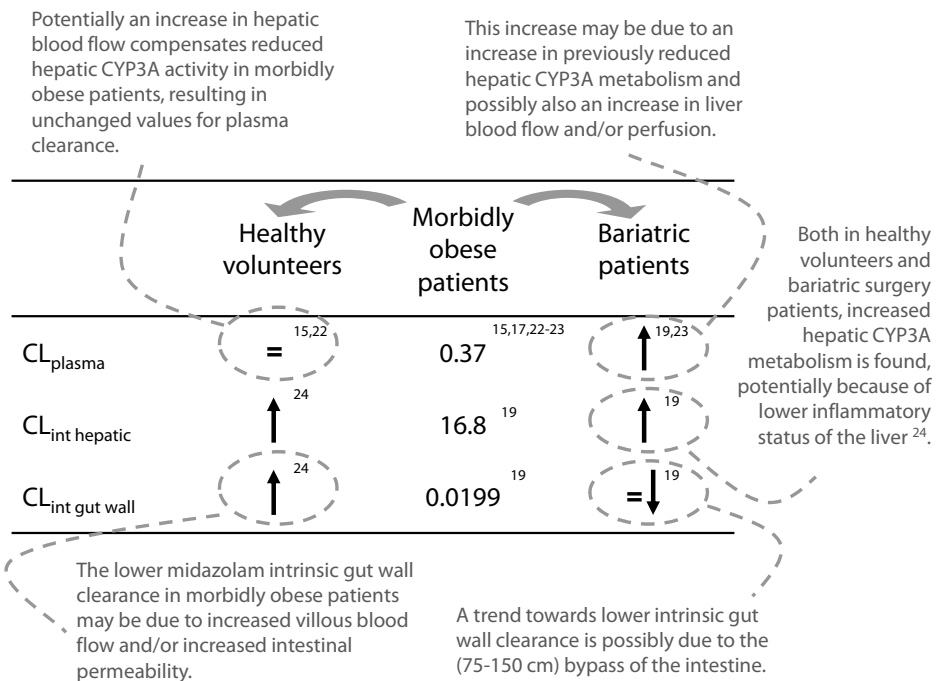


Figure 1 An overview of results on midazolam plasma clearance (CL_{plasma} (L/min)), intrinsic blood clearance at the level of the gut wall ($CL_{\text{int gut wall}}$ (L/min)) and intrinsic blood clearance at the level of the liver ($CL_{\text{int hepatic}}$ (L/min)) in morbidly obese patients in comparison to healthy (non-obese) volunteers and bariatric patients. The results are taken from Chapters 5, 6 and 7 and literature²²⁻²⁴. The grey arrows indicate the direction of comparison.

hepatic CYP3A activity (that is related to morbid obesity), but that at the same time another non-CYP3A related process is involved in an increase in midazolam plasma clearance (Chapter 6) ¹⁷. This other process may be an increase in hepatic blood flow (Q_H) or hepatic perfusion ²¹. An increase in Q_H in morbidly obese patients in comparison with healthy volunteers may also explain the similar midazolam plasma clearance in morbidly obese patients in comparison with healthy volunteers, despite reduced hepatic CYP3A activity related to morbid obesity (Chapter 5 and Figure 1) ¹⁵.

In conclusion, a semi-PBPK model was identified that adequately described midazolam and CYP3A mediated 1-OH-midazolam concentrations after both oral and intravenous administration. Using this model it was found that in patients one year after bariatric surgery CYP3A hepatic intrinsic metabolizing capacity is increased in comparison to morbidly obese patients before bariatric surgery. However, CYP3A mediated gut wall intrinsic clearance shows a trend towards lower values in bariatric patients, probably as a result of the 75-150 cm bypass of the initial part of the small intestine.

PERSPECTIVES

How to get to evidence-based dosing in morbidly obese or bariatric patients

In this thesis, two drugs have been studied using well-designed clinical trials resulting in evidence-based dosing recommendations for morbidly obese and bariatric patients (see **Appendix I**). However, to establish evidence-based dosing for morbidly obese patients before and after weight loss surgery for every clinically used drug separately, as we did in this thesis, will be time and cost consuming. Hence, an intriguing question is how we can accelerate and facilitate this process. One way would be to evaluate whether the PK models that were developed for specific drugs as we did in this thesis may contain information that can be considered system specific information for this population. Such system specific information may potentially be used for predictions for other (unstudied) drugs.

This concept has been explored earlier for both UGT2B7 glucuronidation and renal elimination in neonates and children ²⁵⁻³¹. These studies showed that the covariate function for a population characteristic (e.g. body weight) derived for one so called model drug was predictive for the changes in clearance of another drug cleared through the same pathway. For changes in clearance of the UGT2B7 substrate zidovudine in young infants, the same influence of body weight was found as for the UGT2B7 substrate morphine and potentially other substrates of UGT2B7 ^{28-29, 32}. Also, for drugs cleared via glomerular filtration, it was found that the covariate model for amikacin clearance in the heterogeneous group of preterm and term neonates was able to describe the clearance

of other glomerularly filtrated drugs such as netilmicin, vancomycin, tobramycin, and gentamycin across this population^{27,30}.

For obese patients, we tended to apply a similar approach for which the literature overview of Chapter 2 was written. In fact, this overview showed coherent trends of the influence of obesity on the different classes of clearance pathway. However, the observed trends should be prospectively evaluated before they can be used to predict the impact of obesity on an unstudied drug. This particularly applies to morbidly obese individuals, because the studies in the review predominantly included overweight and obese patients as opposed to morbidly obese patients.

In this thesis, we found for cefazolin (Chapter 4) which is mainly eliminated by glomerular filtration (GFR) and active tubular excretion¹¹, that there was no influence of body weight on clearance. Also for the CYP3A substrate midazolam (Chapter 5), no effect of morbid obesity on clearance was found in comparison to healthy volunteers. A crucial question in this respect is whether these results can be applied to other renally cleared and CYP3A metabolized drugs, respectively. The review in Chapter 2 shows that of the ten studies involved in glomerularly filtrated drugs, six studies show a significant increase in clearance and four studies show no difference, indicating that the influence of morbid obesity on glomerular filtration may not be straightforward to predict. This is in line with studies reporting that both GFR hyperfiltration and impairment may be present in the general morbidly obese patient population, with impairment reported particularly upon a prolonged state of morbid obesity³³⁻³⁵. As such it seems that our findings for cefazolin are in agreement with literature as we report unchanged cefazolin clearance in a morbidly obese patient group that was relatively young (mean age 40 years) with normal creatinine concentrations at inclusion of the study.

The lack of difference in clearance of the CYP3A substrate midazolam between morbidly obese patients and non-obese volunteers (Chapter 5) seems to be in contrast with the results of the review of Chapter 2 in which several studies showed significantly lower oral clearance (CL/F) of CYP3A mediated drugs. However, as we found a higher midazolam oral bioavailability (F) in morbidly obese patients in comparison to healthy volunteers (60 versus 28%, respectively), indeed a lower CL/F for midazolam in morbidly obese patients can be reported. Using a more sophisticated approach in Chapter 7 (using semi-PBPK model for midazolam and 1-OH midazolam), a lower CYP3A metabolizing capacity of the liver was found in morbidly obese patients in comparison to non-obese healthy volunteers from the literature. This reduced CYP3A activity in morbidly obese patients is in good agreement with results of *in vitro* and animal studies showing reduced CYP3A protein expression and activity³⁶⁻³⁹. Despite this reduced CYP3A activity in the liver, similar plasma clearance values for morbidly obese and non-obese individuals were found (Figure 1, Chapter 5&7). As a consequence, it is hypothesized that another process (e.g. liver blood flow, liver perfusion and/or size of the liver) compensates for this

reduction in hepatic CYP3A metabolizing capacity. It therefore seems that for the success of between drug extrapolation per pathway information on obesity-related changes in liver blood flow, size and perfusion are needed. Future studies should therefore not only focus on the quantification of the influence of obesity on drug different metabolism and elimination pathways using model drugs, but also on the quantification of changes in liver blood flow, size and liver perfusion to be able to make better informed predictions on how plasma clearance of an unstudied drug will change with obesity. In this respect, also the hepatic extraction ratio of a drug may play a role ⁴⁰, as plasma clearance of low extraction ratio drugs are more sensitive to changes in metabolizing activity of the involved enzyme system and high extraction ratio and drugs are more sensitive to changes in the blood flow (Chapter 7, Figure 5).

The studies reported in this thesis show that particularly the volume of distribution of the two drugs studied are impacted by morbid obesity. Jain *et al.* showed that the influence of obesity on hydrophilic drugs may be predicted based on the Log P value, while for (highly) lipophilic drugs no such trends can be observed ⁴¹. As the change in distribution volume for the two drugs studied in this thesis were responsible for the proposed dose adaptations for morbidly obese patients (Appendix I), concepts to predict the influence of obesity on volume of distribution are needed. Volume of distribution is determined by drug characteristics, including protein binding, transporter dependency, the ability to cross tissue membranes, binding within blood and tissues and partitioning into fat ⁴⁰. In addition, volume of distribution is determined by systemic properties of which in particular blood volume, adipose tissue volume, cardiac output and tissue perfusion are impacted by obesity ^{21, 42-43}. Theoretically, when the influence of obesity on the systemic parameters governing volume of distribution are known and drug characteristics are known, it should be possible to predict the change in volume of distribution for a specific drug in a specific obese individual. Huisinga *et al.* have proposed such a model for estimating volume of distribution at steady state (V_{ss}) based on the concept that adipose tissue volume equals total body weight (TBW) minus lean body weight (LBW) ⁴⁴:

$$V_{ss} = V_{s,ref} \times \left((1-R) \times \frac{LBW}{LBW_{ref}} + R \times \frac{TBW - LBW}{TBW_{ref} - LBW_{ref}} \right)$$

in which LBW is the lean body weight (estimated by the formula of Janmahasatian *et al.* ⁴⁵), '*ref*' indicates the reference individual (a non-obese healthy volunteer age 20-50 years) and R denotes the adipose-to-total volume of distribution ratio of the reference individual which can be estimated from clinical data ⁴⁴. A drawback of this model seems that the value R comprises all drug characteristics and needs to be determined for each drug individually. Therefore, the applicability of this model is unclear at this point and

should be subject of future studies. Alternatively, physiological models in which drug characteristics regarding drug distribution can be defined (e.g. log D, ionization at pH 7.4, protein binding, tissue partition coefficients, etc.) seem more promising as opposed to a single drug parameter. Currently, several software packages of such physiologically based pharmacokinetic (PBPK) models are available, including SimCYP®^{20, 46}, which deserve to be explored for their predictive value to estimate volume of distribution in (morbidly) obese individuals.

The PBPK software package SimCYP® also proved capable of mimicking observed clearance values in (morbidly) obese patients for 6 out of 8 compounds in 60-100% of the simulations using the 'obese' and 'morbidly obese' population of this program⁴⁷. However, for 2 compounds (phenytoin and clorzoxazone) clearance predictions were in good agreement for only 20% of the simulations⁴⁷, implying that these models need further information, in particular as the exact influence of (morbid) obesity on some physiologic parameters (e.g. hepatic blood flow and perfusion) remains unclear. While this approach seems very promising for predicting the pharmacokinetics of unstudied drugs in (morbidly) obese patients, in our opinion close collaboration with groups performing clinical trials in morbidly obese patients are important to further inform and improve the predictability of these PBPK models.

These concepts for predicting pharmacokinetics in (morbidly) obese patients may also be applied for patients after weight loss (bariatric) surgery. For this population, the type of bariatric surgery, time after bariatric surgery and decrease in body weight should be considered. Darwich *et al.* have aimed to predict the disposition of drugs in patients after different types of bariatric surgeries using an adjusted advanced drug absorption and metabolism (ADAM) model combined with a PBPK model⁴⁸. On the basis of this model, the authors were able to adequately predict the trends in oral drug exposure of atorvastatin and cyclosporine (CYP3A substrates) following a Roux-and Y-gastric bypass surgery⁴⁸. However, this model did not yet include a recovery of hepatic CYP3A metabolizing capacity as indicated by the Chapters 6 and 7. This further underlines the need to perform clinical trials on (model) drugs to inform PBPK models which can then be applied to predict the influence of morbid obesity and bariatric surgery on unstudied drugs. In addition to the recovery of intrinsic hepatic CYP3A metabolizing capacity, knowledge on the change in physiologic parameters due to the reduction in body weight (e.g. cardiac output, liver perfusion, adipose tissue volume, etc.) is needed to further enhance the applicability and predictability of such a PBPK model for patients after weight loss surgery.

In conclusion, on the basis of these concepts the process of getting to evidence-based dosing recommendations for all clinically used drugs for the morbidly obese and bariatric surgery patient population may be accelerated and as such it seems that further study on these concepts are justified.

Tips and tricks for the design and analysis of studies in morbidly obese and bariatric surgery individuals

While additional clinical trials in morbidly obese before and after weight loss surgery are evidently needed, this section aims to emphasize on methods and techniques for future clinical research that ultimately aim to guide dosing in morbidly obese patients before and after weight loss surgery.

First, for future studies it is recommended to measure and quantify the clinical effects (pharmacodynamics, PD) in addition to pharmacokinetics (PK), as in the end it is the clinical effect that will determine the optimal dose for the individual morbidly obese or bariatric patient. In this thesis, the pharmacodynamics of both the drugs that were studied for the PK, have been measured. For cefazolin, the clinical desired effect is the prevention of surgical wound infections. Due to the nature of this clinical endpoint, large trials will be needed to measure the effect of a single cefazolin dose. Therefore, we have evaluated the cefazolin concentrations which are expected to correlate most closely with its antibacterial effect, i.e. the subcutaneous tissue ISF concentrations, in addition to unbound and total cefazolin plasma concentrations (Chapter 4). To date, clinical microdialysis is the only sampling technique that allows for measurement of free, active concentrations in virtually any tissue such as ISF⁴⁹⁻⁵⁰. In addition, clinical microdialysis has been shown to be a safe, reproducible, and an ethically acceptable technique for studying tissue drug distribution in human⁵¹⁻⁵². Alternative methods for measuring tissue concentration include tissue biopsies or blister fluid techniques⁵³⁻⁵⁴. A draw back of these alternative methods is that they do not easily allow for continuous measurements. Furthermore, tissue biopsies are homogenized which prevents the measurement of inter- and intra- cellular concentration separately, while for antimicrobial agents only the inter cellular concentration is of interest, as this fraction is expected to exert an antimicrobial effect. In addition, the blister fluid technique may be quite painful for each blister made for each measurement⁵⁵. In contrast, in case of clinical microdialysis, the insertion of the microdialysis membrane may be considered moderately painful as well, but is only performed once at insertion. After insertion no pain was experienced until the end of the study. So, in the study of Chapter 4, clinical microdialysis facilitated insight into cefazolin target site penetration in morbidly obese patients. It is emphasized that these measurements in the ISF proved crucial for conclusions regarding cefazolin dosing in this patient population as plasma concentrations proved relatively similar while subcutaneous tissue distribution and concentrations were largely reduced in morbidly obese patients in comparison to non-obese patients^{12,14}.

For the midazolam study of Chapter 6, sedation scores were recorded from midazolam oral dose administration until 160 ± 48 minutes after dosing. In Figure 2, the Richmond Agitation and Sedation Scale (RASS) scores are shown for morbidly obese patients before (occasion 1) and one year after bariatric surgery (occasion 2). For occasion 1, 10 out

of 19 morbidly obese patients were sedated to some extent (score -1 and/or -2), while 9 out of 19 patients showed no sign of sedation (RASS = 0). One year later, 16 out of 18 patients showed some level of sedation (score -1 to -4), while only 2 patients showed no level of sedation. Moreover, sedation was deeper after bariatric surgery (maximum of -4 reported in 4 patients) compared to before bariatric surgery (maximum of -2 in 2 patients) and seemed to occur slightly faster. The sedation levels versus times profiles suggest that the midazolam concentration-time profile is indicative of its sedative effect in morbidly obese patients before and after bariatric (Figure 2). However, it should be noted that the less deep sedation levels observed in morbidly obese patients before bariatric surgery may also be the result of anxiety related to the surgical procedure that may be experienced by these patients while one year after surgery no surgical procedure

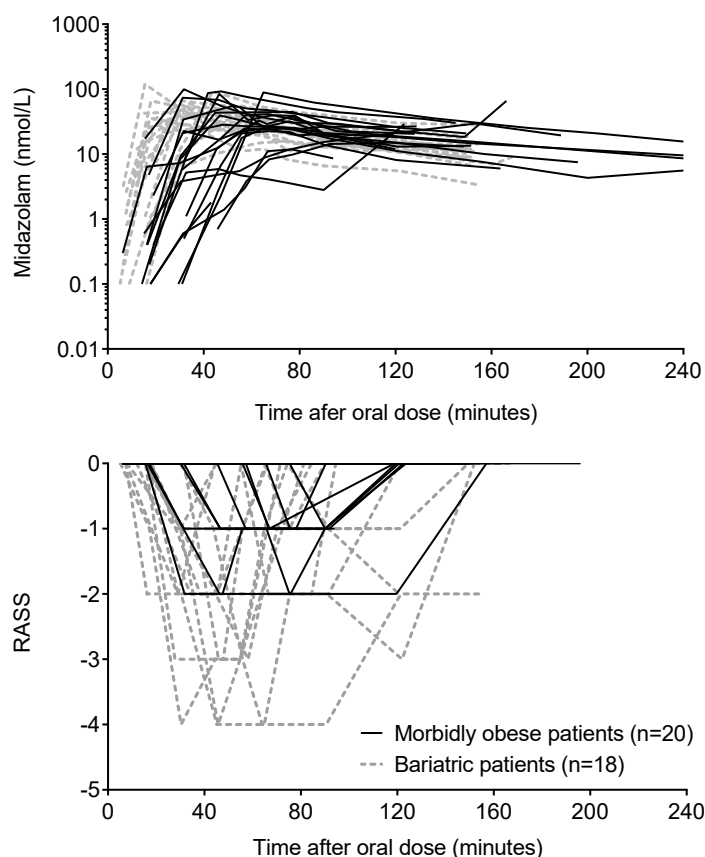


Figure 2 Midazolam concentration versus time (upper panel) and Richmond Agitation Sedation Scale (RASS) scores over time (lower panel) after a 7.5 mg oral midazolam dose in 20 morbidly obese patients before (black lines) and 18 patients one year after bariatric surgery (grey dotted lines) from the study described in Chapter 6.

was scheduled. In conclusion, for both of the drugs studied in this thesis, drug effects have been measured in addition to pharmacokinetic profiles, which may provide a more profound basis for dose recommendations in morbidly obese and bariatric surgery patients.

Second, it is recommended to evaluate the pharmacokinetics after both oral and intravenous administration in order to estimate the influence of morbid obesity or bariatric surgery for each PK parameter separately (i.e. oral bioavailability (F), clearance (CL) and volume of distribution (V)). In studies in which the drug is administered orally, only the apparent clearance (CL/F) and volume of distribution (V/F) can be determined, while studies on intravenous administered drug result in estimates of CL and V and not of F. In particular because the majority of pharmacotherapy is given orally, knowledge on how F or CL are each impacted by morbid obesity or bariatric surgery is essential for the extrapolation of the results to other drugs as described in 8.2.1.. For this reason in Chapter 5 and 6, a semi-simultaneous oral-intravenous dosing design was applied. Earlier, it had been shown that this semi-simultaneous dosing design method is a reliable and accurate for estimating oral bioavailability (F) and systemic clearance (CL) in a single person, on a single occasion⁵⁶⁻⁵⁹. Alternatively, the stable isotope method for determining oral bioavailability in a single person on a single occasion may be applied⁶⁰. However, the preparation of the labeled drug and the determination of the labeled drug in the samples may be expensive and labor intensive. In conclusion, a semi-simultaneous dosing design allows for separate estimation of both CL and F (Chapter 5 and 6) and therefore also of hepatic and gut wall CYP3A mediated metabolism (Chapter 7).

Third, when designing a clinical trial the choice of control or reference group determines the type of results and conclusions that can be drawn from the trial. In this thesis, different types of control groups have been used: non-obese (never been obese) patients undergoing a Toupet fundoplication laparoscopic procedure (Chapter 4), healthy (never been obese) volunteers (Chapter 5) and the same patients (who were morbidly obese at the time) one after year a bariatric surgery (Chapters 6 and 7). Besides the specific advantages and drawbacks of each type of control group, it can be expected that comparing two groups does not allow for estimation of a continuous covariate function, but rather a binary function ('obese/non-obese'), to describe the influence of overweight or obesity, while in fact the overweight itself (normal weight to super obese) may be expected to be a continuous parameter. For instance, when analysing midazolam PK in morbidly obese patients versus healthy volunteers (Chapter 5) a large difference in oral bioavailability (F) was found, which was defined by a binary covariate, 'obese/non-obese'. Whether and how midazolam F changes with increasing degree of overweight or obesity remains unclear as no midazolam concentrations in individuals in between healthy volunteer and morbidly obese were available. Following this, it can be expected that the predictability of midazolam oral bioavailability by this particular

lumped into an empirical three compartment population PK model. In addition, further simplification of the model was performed assuming quasi steady state approximation as outlined in Supplement 2 of Chapter 7⁶⁵. This model simplification allowed omitting setting values for the organ volumes of the gut wall, liver and portal vein, while giving approximately the same model prediction (Supplement 2 of Chapter 7). Ultimately, this model only requires knowledge on hepatic and villous blood flow and protein binding of the population studied to estimate midazolam clearance at the level of the gut wall and liver. For future projects, semi-PBPK modeling may be applied to estimate intrinsic metabolizing capacity in special patient populations providing insight at what level (blood flow, protein binding, intrinsic metabolic capacity, etc.) drug clearance is impacted by obesity or bariatric surgery and thus enhancing the extrapolation potential of the results.

Finally, in future trials physiological parameters should be collected in order to understand the observed changes in the pharmacokinetics and to enhance the applicability of PBPK models. The conversion of the influence of obesity on CYP3A activity in the liver to plasma clearance of midazolam and other CYP3A substrates as reported in the Chapters 6 and 7, show the relevance of obesity related changes in the physiology of the obese individual. For instance, hepatic blood flow is an important physiological parameter involved in the clearance of many medium and high hepatic extraction rate drugs (e.g. midazolam). Yet, it is still unclear whether and how hepatic blood flow changes with obesity and bariatric surgery. It has been reported that cardiac output increases with (morbid) obesity⁶⁶ and that the percentage of cardiac output going to the hepatic blood flow is similar to (predicted) normal weight individuals²¹. Furthermore, studies on the pharmacokinetics of propofol, a high extraction ratio drug and therefore considered a marker of hepatic blood flow⁶⁷, indicate a 0.75 allometric increase in hepatic blood flow with body weight⁶⁸⁻⁶⁹. In contrast, a study in animals shows that hepatic blood flow and perfusion (hepatic microcirculation) reduce with the degree of fatty infiltration in the liver, a condition which is highly associated with (morbid) obesity⁷⁰⁻⁷¹. Moreover, data on hepatic blood flow values in bariatric patients are non existent. This lack of information prevents a full understanding of the change in midazolam clearance observed in bariatric patients in comparison to morbidly obese patients (Chapter 7). Therefore, we recommend that in future clinical trials in morbidly obese and/or bariatric patients physiological parameters should be measured in order to enlarge the predictability and extrapolation potential of the results from clinical trials to other (unstudied) drugs. Lastly, it should be noted that the collection of such physiologic parameters may not be easy, as not all methods (e.g. Flo Trac/Vigileo™ for measuring cardiac output) have been validated in the (morbidly) obese population and may therefore be inappropriate.

In conclusion, the most efficient way towards evidence-based dosing in morbidly obese and bariatric patients is to perform optimally designed clinical trials in morbidly obese and bariatric patients, to investigate how system specific properties (e.g. CYP3A activity) can be inferred from these trials and to evaluate whether these system specific properties may predict the impact of obesity and weight loss surgery on other (unstudied) drugs. The clinical studies should be designed to include the complete range overweight to super obese patients (BMI 25 – 100+ kg/m²) and in case of bariatric surgery, various types of bariatric surgery and periods after the bariatric procedure. Within these clinical trials one should aim to collect data on concentration-time profiles (pharmacokinetic data, PK), clinical effects (pharmacodynamic data, PD) as well as physiological parameters (e.g. blood flows, protein binding, etc.). Finally, PBPK(-PD) models which allow for the integration of pharmacokinetic and physiologic parameters and possibly also pharmacodynamic parameters for the obese and bariatric patients population should be further developed to improve prediction of the impact of obesity and bariatric surgery on unstudied drugs. With this thesis we hope to have contributed to this relevant topic.

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