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The impact of obesity on the pharmacokinetics of drugs in adolescents and adults

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Chapter 1

Scope and intent of
the investigations



Worldwide prevalence rates of overweight (BMI > 25 kg/m²) and obesity (BMI > 30 kg/m²) have increased substantially between 1980 and 2013 for both adults (28%) and children (47%)¹, with the highest increase in the adult population observed in the USA, UK and Australia. In the USA, roughly a third of men and women were obese in 2013, while estimated prevalence rates between 30-69% are reported in the Middle East (Qatar, Kuwait, Saudi Arabia), Africa (Libya, South Africa and Egypt) and Oceania countries¹. In Western Europe, the prevalence rates are lower with an average of 21%, with the lowest prevalence rates in the Netherlands, including 13% obese men and 16% obese women in 2013¹.

Even more alarming are the percentages of overweight or obesity in children and adolescents, with 34.5% and 20.5% of the American adolescents (12-19 years) being overweight (BMI for age ≥ 85th percentile) or obese (BMI for age ≥ 95th percentile), respectively, in 2011-2012². In addition, high rates of obese adolescents are also reported in countries in Middle East, North Africa, Caribbean and Oceania¹. Childhood obesity is particularly worrisome, as obese children are likely to become (morbidly) obese adults. Obesity is an important risk factor for the development of cardiovascular disease^{3,4}, type 2 diabetes^{4,5}, non-alcoholic fatty liver disease (NAFLD)⁶ and certain cancers⁷ and as such the obese population may require frequent pharmacotherapy or surgical intervention. Many of the metabolic and cardiovascular complications of obesity may already be present in obese children⁸⁻¹⁰.

When a pharmacological treatment in an obese patient is initiated, the expected physiological changes upon obesity should be considered in relation to the properties of the drug itself. Among others, these changes include an increase in both fat- and lean body weight (LBW), with the increase in fat mass being larger than the increase in LBW as LBW accounts for 20-40% of the excess weight¹¹. Moreover, an increased cardiac output, circulating blood volume^{12,13}, and glomerular filtration rate (GFR)^{14,15} are reported. The increased GFR is associated with an increased renal plasma flow, resulting in hyperfiltration, which, in a later stage, can eventually lead to glomerular damage and ultimately in a decrease in renal function^{14,15}.

Obesity can also have an influence on the activity of hepatic enzymes responsible for metabolism of drugs¹⁶. For example, in vitro and obese rodent studies showed a reduced CYP3A protein expression or activity with obesity¹⁷⁻²⁰, while a higher CYP2E1 protein expression or activity is reported²¹⁻²³. Moreover, an increased CYP2E1 activity²⁴ or CYP2E1 protein expression is reported in liver biopsies from obese patients with or without measured NAFLD²⁵⁻²⁷. In vitro research reported no changes in UGT activity of acetaminophen in human liver tissue samples diagnosed with NAFLD²⁸, even though an increased UGT protein expression is reported in obese rats²⁹. The influence of obesity on the expression or activity of renal transporters, responsible for tubular secretion and

reabsorption of drugs, is largely unknown. Obese mice showed no difference in mRNA expression of organic cation transporters (OCT) 1 and 2, although other mice studies showed a decrease in the OCT2 and multidrug and toxin extrusion protein 1 (MATE1) transporter³⁰⁻³³.

NAFLD might be the underlying cause of the changed CYP2E1 and CYP3A4 expression in obesity^{20,34}. More specifically, CYP3A expression can be decreased upon infiltration of macrophages and adipocytes into the adipose tissue excreting inflammatory cytokines, which can repress the transcription of CYP3A^{20,35-38}. NAFLD refers to a large spectrum of conditions ranging from fatty liver to nonalcoholic steatohepatitis (NASH) and cirrhosis⁶. It is reported that 60-70% of the obese population has simple steatosis, while 18.5-20% of the obese population has even developed NASH³⁹. In children, the prevalence rate of NAFLD is 9.6% in the US⁴⁰, while in obese children a percentage of 38% is reported⁴⁰, although other studies reported prevalence rates between 44-83%⁴¹⁻⁴³. There is hardly any knowledge about the exact changes in physiology in (morbidly) obese children and adolescents or on the enzyme activity and transporters.

The physiological changes occurring upon obesity can have an influence on the pharmacokinetic (PK) parameters of drugs. Various CYP3A substrates showed a reduced oral clearance in obese subjects compared to non-obese subjects¹⁶. In obese patients, glucuronidation and CYP2E1-mediated clearance is expected to be induced^{16,24,44-46}. Moreover, studies on intravenous procainamide, ciprofloxacin and cisplatin, which are all primarily eliminated by tubular secretion, showed a higher clearance in obese adults compared with non-obese adults¹⁶. Since these drugs are transported by the renal OCT system, it can be speculated that the activity of the OCT transporters is induced with obesity. To date, no information is available on the impact of obesity on CYP3A- or CYP2E1- mediated clearance or on tubular processes in obese adolescents, while glucuronidation is likely to be induced in obese adolescents^{16,45}.

Despite the increased number of obese patients and increased pharmacotherapy among these patients, evidence based dosing guidelines are largely lacking, particularly for morbidly obese adults (BMI > 40 kg/m²) and obese children and adolescents (BMI for age ≥ 95th percentile). For these special populations, PK studies are needed to develop evidence based dosing guidelines. These studies can subsequently be used to hypothesize what physiological changes may occur in obesity leading to these results. Particularly for obese children and adolescents, adequate PK studies are lacking^{47,48} and dosing guidelines are based on retrospective data comparing drug dosing in obese children vs. non-obese children^{49,50} and on extrapolation from dosing guidelines for obese adults^{49,51}. Therefore, the aim of this thesis is to study the pharmacokinetics of drugs

in obese adolescents and morbidly obese adults with a special focus on midazolam, acetaminophen and metformin.

For this purpose, in Section I we report in **Chapter 2** on the quantification of the obesity-related changes by presenting a literature overview of published equations for the PK parameters clearance and volume of distribution in pharmacometric studies in obese individuals. In addition, general information about currently used body size descriptors and future directions for the execution of clinical trials and modelling in (morbidly) obese patients are given. **Chapter 3** is focusing on the current knowledge on the physiological changes in obesity with the resulting changes in drug disposition, i.e. the influence of obesity on oral bioavailability, absorption rate, drug distribution, metabolism and excretion. Moreover, special attention is paid to the complex population of obese children and changes in drug disposition in this population.

In Section II we report the results of clinical studies in obese adolescents. Clinical trials and pharmacometric analyses are particularly important in obese children and adolescents, as guidelines are lacking for this population and currently used paediatric dosing algorithms expressed in mg/kg may lead to overdosing⁵². In these analyses the evaluation of the influence of (over)weight on PK parameters in obese children is complicated by the interrelation between growth, age and obesity, i.e. with increasing age body weight may increase as a result of growth, obesity or both⁵². This aspect is evaluated in Chapters 4 (midazolam) and 5 (metformin). **Chapter 4** is evaluating the pharmacokinetics of midazolam and its metabolites 1-OH-midazolam and 1-OH-midazolam glucuronide in obese adolescents upon an intravenous bolus dose that was given before surgery. Midazolam is a commonly used lipophilic benzodiazepine for preoperative sedation in paediatric anaesthesia because of its potent sedative, amnesic and anxiolytic properties. It is a CYP3A probe drug, since it is extensively metabolized by CYP3A to its metabolites⁵³. CYP3A is an important enzyme, since it is responsible for the primary metabolism of 25% of the drugs⁵⁴.

Chapter 5 is focusing on the pharmacokinetics of metformin in overweight and obese adolescents. Metformin is a biguanide compound and is registered for the treatment of type 2 diabetes mellitus in paediatric patients above 10 years. Even though a large increase in metformin prescriptions in children and adolescents was observed in the Netherlands between 1998 and 2011⁵⁵, the pharmacokinetics of metformin is not extensively studied in this population. Metformin is not metabolized in the liver, but excreted unchanged in urine. Active tubular secretion is the primary route of renal elimination conducted by OCT and MATE^{30,56-58}. The pharmacokinetics of metformin in obese adolescents were evaluated during an oral glucose tolerance test that was performed as

part of a clinical trial on the long term effects of metformin vs. placebo in obese children with insulin resistance.

In Section III we report the results of clinical studies in morbidly obese and non-obese adults with midazolam and acetaminophen. As mentioned above, midazolam is used as a CYP3A probe drug. CYP3A is located both in the liver and intestines and as such the activity of CYP3A is important for both midazolam clearance and oral bioavailability^{59,60}. To distinguish between oral bioavailability, systemic clearance and volume of distribution, oral and intravenous administration should preferably be combined in a single study, i.e. in a semi-simultaneous study design. For midazolam, these non-obese adults are, apart from the combined analysis with morbidly obese patients, first described in a separate study in which the 24-hour variation of midazolam was studied (**Chapter 6**). In this Chapter, midazolam was administered in a semi-simultaneous oral and intravenous manner to twelve healthy volunteers over six different time points at three visits, to evaluate the influence of the time of the day on the PK parameters of midazolam. In **Chapter 7**, the pharmacokinetics of midazolam are reported in morbidly obese adult patients in a combined analysis with the healthy volunteers of Chapter 6 receiving midazolam at the same time of the day as the morbidly obese patients.

Chapter 8 describes the pharmacokinetics of acetaminophen with specific emphasis on the contribution of the different metabolic pathways in morbidly obese patients in comparison to non-obese patients. Acetaminophen is mainly metabolized via glucuronidation and sulphation, while the minor pathway through CYP2E1 is responsible for hepatotoxicity. In obese subjects, the total clearance of acetaminophen is reported to be increased compared to non-obese subjects⁶¹ and as such obese patients may need a higher acetaminophen dose. However, since the CYP2E1-mediated pathway is involved in hepatotoxicity, it is important to explore the separate contribution of the different metabolic pathways to the increased total acetaminophen clearance, especially since the CYP2E1 activity is expected to be induced in obese patients²⁴.

In Section IV, we report upon the combined analysis of obese adolescent and morbidly obese adult populations receiving midazolam. CYP3A is known to vary with age, inflammation and obesity^{16,62-65}. As clearance is typically lower in (non-obese) children compared to (non-obese) adults, allometric scaling with a factor of 0.75 on the basis of body weight is often applied⁶⁶⁻⁶⁸. Particularly for adolescents there is agreement on this approach. The FDA proposed in 2012 that allometric scaling on the basis of adult data without the use of a dedicated pharmacokinetic study is a reasonable approach for scaling to adolescents (>12 years)⁶⁹. However, this approach may be questionable in obese adolescents, as this approach uses body weight as a proxy for size and does not consider obesity. **Chapter 9** may shed light on this issue, by combining the data of

midazolam in obese adolescents (Chapter 4) and morbidly obese adults (Chapter 7) to evaluate the difference in midazolam clearance and explore a model that can be used to consider obesity in the paediatric population.

In **Chapter 10** the results and conclusions of this thesis are summarized and discussed, and future perspectives are presented. In this Chapter, perspectives are given concerning the extrapolation of data from obese adults to obese adolescents, and tools are provided how to evaluate data in obese children and adolescents. Finally, ideas are provided to achieve safe and effective use of acetaminophen in morbidly obese patients in the near future.

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