Unraveling the drivers of antimicrobial pharmacokinetic variability in individuals with obesity and hospitalized patients with multimorbidity

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Part I

CHAPTER 1

1

Introduction

Infectious diseases are common among hospitalized patients as 1 in 3 patients receives treatment with at least one antimicrobial agent[1]. Efficacious treatment of infectious diseases hinges on prompt administration of the right dose of the right drug. In the clinical setting pharmacological therapy is initiated immediately when a (severe) infectious disease is suspected. Selecting the right empirical antimicrobial drug is done by choosing an agent that covers the most likely pathogens given the local epidemiology. After the most appropriate drug is selected the right dose needs to be determined. But how does one determine the right dose for each patient? To determine the optimal dose, knowledge on both pharmacokinetics and pharmacodynamics are needed.

The studies described in this thesis aim at elucidating whether and how various patient characteristics influence concentrations of antimicrobial agents in plasma and how variation in these concentrations translate into effect. In this regard, focus lies on elucidating the influence of (morbid) obesity, (morbid) obesity & critical illness and mucosal barrier injury on drug concentration in plasma. The drugs of interest are the antifungal agent fluconazole and the antibacterial agent ciprofloxacin. For both drugs plasma concentrations are known to correlate with clinical- and microbiological cure and both antimicrobials are widely used in the hospital and community. At present it remains unknown how the pharmacokinetics of these two drugs are influenced by morbid obesity and multimorbidity. As a result, clear guidance for dose adjustment in these special patient populations is unavailable.

Microbes and antimicrobial agents – Fluconazole and Ciprofloxacin

In hospitalized patients infections of the respiratory-, urinary-, and gastro-intestinal tract are frequently encountered and may be caused by a wide range of pathogens.

These causes of infectious diseases remained unknown until Louis Pasteur disproved the spontaneous generation theory of spoilage and fermentation in 1861 when he revealed that invisible microorganisms were the cause[2]. In 1881 this work was followed up by a number of papers describing the germ theory of disease which is the currently accepted scientific theory for infectious diseases[3]. In the meantime, the Norwegian physician Gerhard Armauer Hansen was the first to discover a bacterial cause for an infectious disease, leprosy, when he identified *Mycobacterium leprae* in 1873. The German microbiologist Robert Koch subsequently discovered *Bacillus anthracis* and *Mycobacterium tuberculosis* in 1882 and *Vibrio cholerae* in 1884, which were major causes of infectious diseases at the time[4]. Although the cause of infectious diseases was slowly unraveled, efficacious treatment was impossible because antimicrobial agents were not yet discovered.

The first antimicrobial agent was the arsenic based antibacterial agent arsphenamide which was discovered by Paul Ehrlich and Sahachiro Hata in 1909[4]. Various classes of antibacterial agents have been discovered ever since. The fluoroquinolones are a class of antibacterial agents derived from nalidixic acid which was discovered by George Lesher during an attempt to synthesize chloroquine in 1962. The second-generation fluoroquinolone ciprofloxacin was licensed in 1987[5]. It inhibits bacterial DNA synthesis by blocking DNA-gyrase and topo-isomerase IV which both play a vital role in folding, unfolding, stretching and relaxing of bacterial DNA. Blocking these enzymes ultimately kills the bacterium. Ciprofloxacin is a broad spectrum antibiotic and is mostly used for the treatment of aerobic gram-negative bacteria, especially *Enterobacterales*[6].

The first antifungal agent is nystatin which was licensed in 1954. Since then, similar to antibacterial agents, various classes of antifungals reached the market. Fluconazole is a member of the triazoles and was first licensed in 1990[7]. It induces structural deformation of the fungus by blocking ergosterol synthesis through CYP51 inhibition. Ergosterol is a sterol vital for maintaining cellular integrity of various fungi; its physiological function is similar to cholesterol in mammalian cells. Fluconazole has a fungistatic effect with a broad antimycotic spectrum and is mainly employed for the treatment of *Candida* and *Cryptococcal* infections[8].

Pharmacokinetics, -dynamics and -metrics

The rationale for dosing antimicrobial agents is to aim for exposure that is high enough to treat the causative pathogen while preventing overexposure and thus minimize toxicity[9].

The field of pharmacokinetics studies how drugs move through the body over time. Four processes can be distinguished: absorption, distribution, metabolism and elimination. Absorption of drugs after oral administration takes place in the gastro-intestinal tract and may be influenced by concomitant food or drug intake or mucosal barrier injury as was demonstrated for posaconazole[10]. Distribution of drugs depends on chemical properties like lipophilicity, ionization, protein binding and blood to plasma ratio[11]. Drug distribution may be influenced by the presence of excess adipose tissue which negatively influences the penetration of ciprofloxacin, cefazoline and metronidazole into skin and soft tissue while meningitis increases the penetration of beta-lactam antibiotics into the central nervous system[12-15]. Similarly, patients admitted to the intensive care can be hemodynamically unstable. This requires aggressive fluid resuscitation in order to maintain the blood pressure within acceptable limits which may also influence drug distribution[16]. Metabolism describes the process of chemical reactions altering the molecular structure of a drug which mainly takes place in the liver. Drug metabolism can be inhibited or enhanced as a result of altered enzymatic activity for instance due

to pathophysiological alterations or drug-drug interactions[17]. Elimination describes how the drug and/or its metabolites are removed from the body by for instance renal clearance or intestinal excretion. The rate at which drugs are cleared from plasma may be influenced by patient characteristics like body weight, renal function, hepatic function or (critical) illness[11, 16–18].

Pharmacodynamics describes the balance between (drug) concentration and effect, for instance the killing of bacteria when an antibiotic is present or the increase in heart rate when adrenaline is released into the bloodstream. The likelihood of a patient being cured using a certain dosing regimen depends on both the exposure to the antimicrobial agent, the susceptibility of the causative pathogen towards the employed antimicrobial agent and the capacity of the host immune system. The susceptibility is expressed as the minimal inhibitory concentration (MIC) i.e. the minimal drug concentration at which in vitro pathogen growth is inhibited within a defined period of time[9].

The MIC is commonly correlated to an exposure target that is predictive for clinical or microbiological cure. Three different exposure/response-relations, often referred to as pharmacokinetic/ pharmacodynamic (PK/PD) targets, are distinguished for the prediction of clinical outcome 1) The percentage of time within a 24 hour period the concentration is above the MIC ($T_{>MIC}$) or time dependent antimicrobials 2) The ratio of the peak plasma concentration and the MIC (C_{max}/MIC) or concentration-dependent antimicrobials 3)The ratio of the area under the concentration-time curve (AUC) and the MIC (AUC/MIC) or concentration and time-dependent antimicrobials[9].

Which exposure/response relation is best associated with clinical outcome may be studied in animal, in-vitro or patient studies. Based on this relation a PK/PD target is formulated that takes both exposure and pathogen susceptibility into account. This PK/PD target can ultimately be used to design dosing regimens for patient populations that have altered absorption, clearance or volume of distribution. For fluconazole an unbound (*f)* fluconazole *f*AUC_{24h}/MIC>100 is associated with clinical outcome for the treatment of invasive candidiasis[19]. For ciprofloxacin an AUC/MIC>125 is associated with probabilities of microbiological- and clinical cure of 86% and 81%, respectively[20]. Even though it remains unknown if these PK/PD targets are readily applicable to individuals with obesity or hospitalized patients with multimorbidity we propose exposure matching as a strategy. Doses are adapted in a special patient population of interest, aiming at an exposure that is similar to a reference population. This strategy has been adopted for tobramycin, gentamycin and vancomycin in individuals with obesity and even critically ill individuals with obesity in case of gentamicin and vancomycin[21 – 25].

Although many antimicrobial agents generally have favorable toxicity profiles, the above described PK/PD target rationale provides a lower-limit of exposure in order to optimize efficacy. Nevertheless, potential toxicity should also be taken into account when designing dosing strategies. Exposure thresholds (expressed as AUC or trough-concentration) may correlate with the development of toxicity and can be considered upper-limits of safety and should also be taken into account.

Pharmacometrics is the interdisciplinary field at the intersection of pharmacology, mathematics, statistics, and computer science, focused on quantifying and optimizing drug therapy through modelling approaches. It is an established tool for analyzing population pharmacokinetic data as it utilizes mathematical models to describe the pharmacokinetic processes within the human body. A population pharmacokinetic analysis is required for new drug applications to quantify pharmacokinetic variability within a population[26 – 28].

A pharmacokinetic model consists of algebraic equations for parameters such as bioavailability, volume of distribution and clearance while accounting for different sources of random variability (interindividual and residual variability). The main aim is to build a model that both describes and predicts the observations made in the study population, which could be focused on pharmacokinetic endpoints describing drug concentration in plasma or tissue over time or pharmacodynamic endpoints like killing of bacteria or fungi. During the modelling process, patient characteristics of interest (e.g. body weight, renal function, hepatic functioning, age or gender) are tested for associations with model parameters. A stepwise approach with regard to testing patient characteristics allows for discrimination between, and characterization of, the influence of for instance renal function on clearance and body weight on clearance.

If the pharmacokinetic model is improved using certain patient characteristics, these can subsequently be used to guide dosing for individual patients. To this end, simulations with the final pharmacokinetic model are made for (large numbers of) virtual patients with a distribution in the patient characteristics that matches the patient characteristics of the studied population. Using this approach, various dosing regimens can be evaluated and those that result in an acceptable exposure, i.e. that provide sufficient likelihood of therapeutic success while assuring the likelihood of toxicity stays within acceptable limits, can be employed in patient care.

In short, pharmacometric approaches can be used to determine if dosing regimens need to be adapted to specific patient characteristics by integrating data and information from clinical trials, preclinical experiments, and real-world patients. Pharmacometricians develop models to predict exposure in diverse patient populations. These models

enable the design of optimal dosing strategies, especially in special patient populations like children, elderly, individuals with obesity, renal- or hepatic impairment or other (multi) morbid pathophysiological conditions.

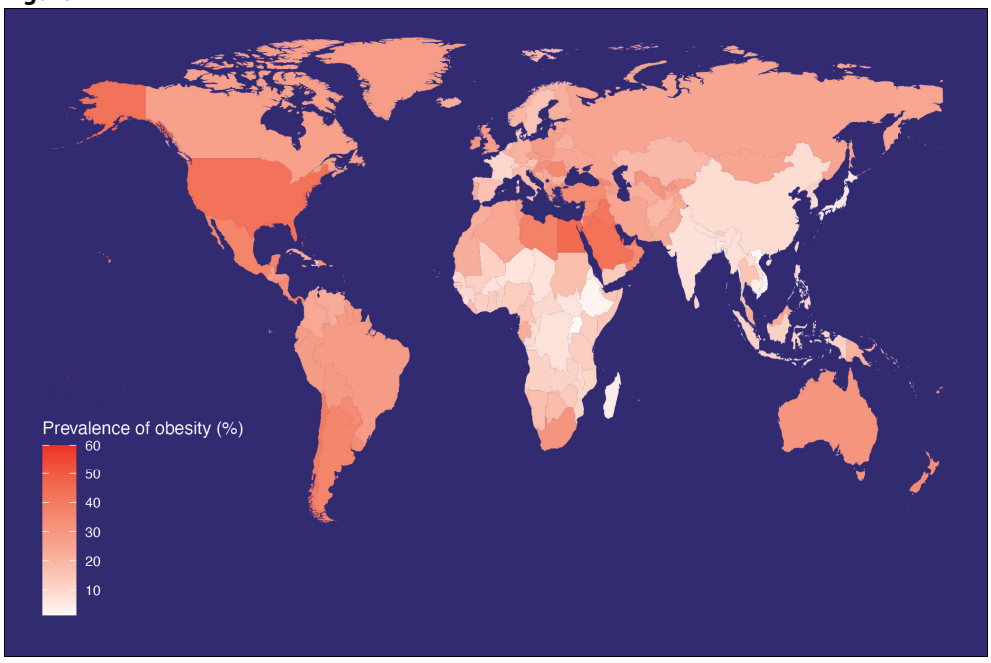
Obesity and multimorbidity – implications for optimal dosing regimens

Obesity is characterized by a disproportionate body weight for height with an excessive accumulation of adipose tissue that is usually accompanied by mild systemic inflammation[29]. The global obesity prevalence reached the questionable milestone of 1 billion people in 2022 (~13% of the global population). It's prevalence tripled since 1975 for women while it quadrupled over the same period for men[28, 29]. Although the prevalence increases globally, large regional differences occur as is presented in figure 1.

Individuals with obesity are more likely to develop comorbidities like hypertension, diabetes, coronary artery disease, heart failure, atrial fibrillation, various types of cancer, stroke and infectious diseases[29]. Overweight or obesity may be quantified using the body mass index (BMI) which is calculated by dividing body weight in kilograms by the square of the height in meters. A BMI 25-30kg/m^2 is considered overweight (or Class 1 obesity) while a BMI 30-35 kg/m^2 is considered moderate-risk obesity (Class 2). The high-risk group are the individuals with a BMI >40kg/m^2, or >35kg/m^2 in the presence of obesity-related comorbidities like diabetes mellitus type II, hypertension, cardiorespiratory conditions (Class 3)[31]. Although this classification only goes up to class 3, obesity may even be viewed on a continuous scale as BMI's up to, and even beyond, 70kg/m^2 may be encountered.

The increased fat mass in individuals with obesity may have implications for selecting the optimal dosing regimen. Increased fat mass may influence pharmacokinetics, especially when these patients also have other comorbidities like reduced renal or hepatic functioning or critical illness which may independently influence metabolism and elimination[16, 24, 25]. Nevertheless, multimorbidity may also be encountered in normal weight individuals, for instance in patients with hematological malignancies with mucosal barrier injury which could influence the absorption of orally administered drugs[10].

Figure 1



The global prevalence of obesity (BMI >30kg/m^2) combined for men and women shows large regional differences. The figure is based on data from 2022 from the NCD Risk Factor Collaboration[30].

To determine the optimal dose for a specific patient (population) it is vital to capture the influence of the specific health condition(s) on the pharmacokinetic process of interest[27, 28]. To guide dosing in individuals with obesity, patients undergoing bariatric surgery are often studied to determine the influence of body weight on pharmacokinetics. An important strength of studying this population is that it allows dense sampling as these patients are already managed with an intravenous line and study procedures can be planned upfront. Moreover individuals with class 3 obesity are frequently encountered in the bariatric surgery population while patients with extreme body weights are relatively scarce among the clinical population. Collecting PK-data in individuals with these extreme body weights allows for precise characterization of the influence of body weight on pharmacokinetic parameters. Bariatric patients are typically otherwise healthy, have good renal function and are often relatively young. Carrying out pharmacokinetics studies in this population prevents any influence of for instance renal replacement therapy which may be encountered among hospitalized patients with obesity and infectious diseases. A theoretical drawback to using bariatric surgery patients to test the influence of obesity on pharmacokinetics is the fact that these patients require surgery. However, as blood loss is minimal (usually <100ml) during these short laparoscopic interventions (±45 minutes), and blood pressure is tightly

monitored during the procedure, the influence of the surgery itself on pharmacokinetics is considered minimal.

Generalization of results from bariatric surgery patients to hospitalized patients with obesity and multimorbidity may be complicated by differences in the presence or distribution of covariates [16]. To ensure applicability of results found in bariatric surgery patients with class 3 obesity to the clinical population of patients with obesity, the model may be enriched with data from obese individuals with multimorbidity that are representative for the clinical population. The results from bariatric surgery patients can be used as a starting point when testing the influence of other patient characteristics on pharmacokinetic parameters based on the data from the clinical population. This approach facilitates assessment of the influence of other potentially relevant covariates like renal function, and admission to the ward or ICU[24, 25].

Aims and scope of this thesis

In this thesis we aim to characterize the influence of obesity on fluconazole and ciprofloxacin pharmacokinetics. Guidance on whether, and how, doses should be adjusted in this population is currently lacking. Ultimately, the results for these two antimicrobial agents are viewed in a broader context comparing our results with previous studies on the influence of body weight on the pharmacokinetics of other antimicrobial agents. Ciprofloxacin pharmacokinetics was subsequently studied in two other subpopulations with multimorbidity, i.e. patients with mucosal barrier injury secondary to the treatment of a hematological malignancy and patients with obesity admitted to the intensive care unit. As for both mucosal barrier injury and ICU admission, the influence on pharmacokinetic parameters is unknown it remains unclear if applying the standard dosing regimens result in sufficient exposure. Within the studies described in this thesis guidance for both fluconazole and ciprofloxacin were designed based on the identified drivers of pharmacokinetic variability.

Results from studies in individuals with (morbid) obesity undergoing bariatric surgery and in non-obese healthy volunteers are described in the first part of this thesis. The influence of body weight on the pharmacokinetics of fluconazole and ciprofloxacin was characterized in two rich sampling studies after both oral and intravenous administration. The results for fluconazole are presented in **Chapter 2**. The results for ciprofloxacin are presented in **Chapter 3**. Individuals with obesity are not currently recognized as a special patient population during drug development. Our view on the clinical implications resulting from the considerable heterogeneity in the influence of weight on clearance between drugs and the importance of taking the labeled dosing strategy (fixed dose versus mg/kg body weight) into account are described in **Chapter 4**.

Studies in hospitalized patients with multimorbidity are described in the second part of this thesis. A cohort of patients with (morbid) obesity admitted to the intensive care unit treated with ciprofloxacin was recruited to determine if additional patient characteristics like renal dysfunction may be needed to predict, and optimize, exposure to ciprofloxacin in the real-world setting of hospitalized individuals with obesity; results are presented in **Chapter 5**.

Besides empirical treatment, ciprofloxacin as oral formulation is often used for gram-negative infection prophylaxis during neutropenia and gastrointestinal mucositis in patients with hematological malignancies. We explored if bioavailability or clearance in this population is affected by mucosal barrier injury which may develop as a complication after preconditioning. Besides studying exposure, we explored whether biomarkers can be used to predict potential differences. Results of this study are presented in **Chapter 6**.

Finally, we summarize and discuss (clinical) implications of our findings, reflect on lessons learned and provide recommendations for future research in **Chapter 7**. Using simulations, we provide a framework for how the recommended future research may be shaped.

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