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

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Citation
Rhee, K. P. van. (2025, February 19). *Unraveling the drivers of antimicrobial pharmacokinetic variability in individuals with obesity and hospitalized patients with multimorbidity*. Retrieved from https://hdl.handle.net/1887/4195405

Version:	Publisher's Version
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UNRAVELING THE DRIVERS OF ANTIMICROBIAL PHARMACOKINETIC VARIABILITY

IN INDIVIDUALS WITH OBESITY AND HOSPITALIZED PATIENTS WITH MULTIMORBIDITY

KOEN VAN RHEE



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

Koen van Rhee

Cover design, lay-out & Printing: ProefschriftMaken | proefschriftmaken.nl

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

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 19 februari 2025
klokke 11:30 uur

door

Koen Patrick van Rhee
geboren te Oldenzaal
in 1989

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The research described in this thesis was performed at the division Systems Pharmacology and Pharmacy of the Leiden Academic Centre for Drug Research (LACDR), Leiden University (Leiden, The Netherlands), the department of Clinical Pharmacology, Tergooi MC (Hilversum, The Netherlands), the department of Clinical Pharmacology, St. Antonius Hospital (Nieuwegein, The Netherlands) and the Clinical research unit of the Radboudumc Technology Center (Nijmegen, The Netherlands).

The research was financially supported by St. Antonius Onderzoeksfonds and Tergooi MC wetenschapsfonds.

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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.

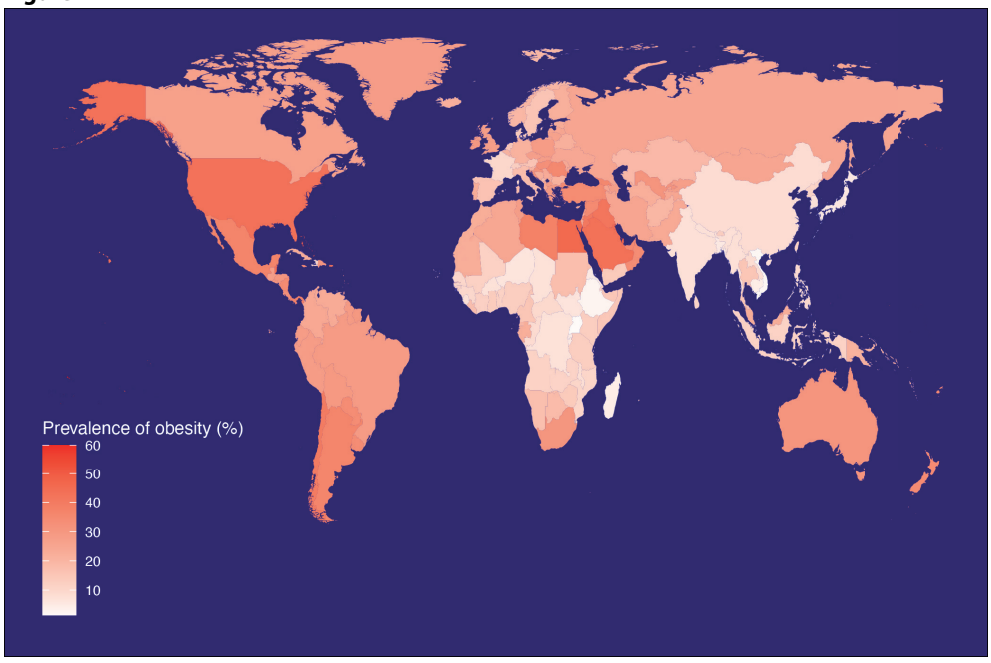
Obesity and multimorbidity – implications for optimal dosing regimens

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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Part II

Antimicrobial pharmacokinetics in individuals with obesity

CHAPTER 2

2

Total bodyweight and sex both drive pharmacokinetic variability of fluconazole in obese adults

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Paul E. Verweij, Paul D. van der Linden, Roger J.M. Brüggemann,
Catherijne A.J. Knibbe



Abstract

Background: Fluconazole is commonly used to treat or prevent fungal infections. It is typically used orally but in critical situations, IV administration is needed. Obesity may influence the pharmacokinetics and therapeutic efficacy of a drug. In this study, we aim to assess the impact of obesity on fluconazole pharmacokinetics given orally or IV to guide dose adjustments for the obese population.

Methods: We performed a prospective pharmacokinetic study with intensive sampling in obese subjects undergoing bariatric surgery (n=17, BMI≥35 kg/m^2) and non-obese healthy controls (n=8, 18.5≤BMI,30.0 kg/m^2). Participants received a semi-simultaneous oral dose of 400 mg fluconazole capsules, followed after 2 h by 400 mg IV. Population pharmacokinetic modelling and simulation were performed using NONMEM 7.3.

Results: A total of 421 fluconazole concentrations in 25 participants (total bodyweight 61.0–174 kg) until 48 h after dosing were obtained. An estimated bioavailability of 87.5% was found for both obese and non-obese subjects, with a 95% distribution interval of 43.9%–98.4%. With increasing total bodyweight, both higher CL and V_d were found. Sex also significantly impacted V_d, being 27% larger in male compared with female participants.

Conclusions: In our population of obese but otherwise healthy individuals, obesity clearly alters the pharmacokinetics of fluconazole, which puts severely obese adults, particularly if male, at risk of suboptimal exposure, for which adjusted doses are proposed.

Introduction

The prevalence of obesity (BMI≥30 kg/m^2) has nearly tripled over the past 50 years[1,2]. Obese individuals often have an increased risk to develop infections, including fungal infections[3-5]. Obesity is known to influence the pharmacokinetics for many drugs and is associated with underdosing of antimicrobials, which may negatively impact clinical outcomes[5-7].

Fluconazole is a widely used antifungal agent to prevent and treat Candida infections, including invasive candidiasis, and superficial infections such as oropharyngeal candidiasis, esophageal candidiasis, candiduria and vaginal candidiasis. Low fluconazole exposure is associated with increased mortality[8,9]. A threshold of $fAUC_{24h}$/MIC>100 is recommended to treat invasive candidiasis[10-12].Due to low plasma protein binding (11%–12%), this can be translated to AUC_{24h}>200 mg*h/L for the Candida clinical breakpoint against fluconazole with MIC equal to 2 mg/L[10].

Fluconazole is available for IV use and as capsules, suspension or tablets for oral administration. In non-obese subjects, the oral bioavailability (F) was reported to be over 90%, but this has not been studied in the obese population[10]. As it is reported that obesity is associated with increased gut permeability and accelerated gastric emptying, it is possible that obesity could influence the oral absorption of fluconazole[7]. Moreover, with fluconazole being primarily cleared renally, its CL could be affected by obesity, which is associated with increased renal flow[7].

A dedicated study on the impact of obesity on the pharmacokinetics of fluconazole, in the absence of other potentially confounding patient characteristics, is lacking. This study characterizes the pharmacokinetics, including the oral F and absorption rate of the capsule formulation, in healthy non-obese and otherwise healthy morbidly obese adults. The results are used to derive model-based dosing recommendations for this special population.

Methods

Study population

Obese adults with BMI>35 kg/m^2 undergoing laparoscopic gastric bypass surgery or sleeve gastrectomy at the St. Antonius Hospital (Nieuwegein, The Netherlands) and non-obese healthy volunteers (BMI 18.5–30.0 kg/m^2) from the Radboud University Medical Center (Nijmegen, The Netherlands), were included. Participants were eligible for inclusion if they were aged 18–65 years. Participants were excluded if they were allergic

to fluconazole or other azoles, pregnant or breastfeeding, taking medication with a known interaction with fluconazole, diagnosed with renal or hepatic dysfunctions, or had a history of long QT syndrome, or drug or alcohol abuse. Written informed consent was obtained before inclusion. This study was approved by the Dutch Medical Research Ethics Committees United (NL66611.100.18) and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines (ClinicalTrials.gov identifier: NCT04122560).

Study design

Participants received a semi-simultaneous oral dose of 400 mg fluconazole as capsules, followed 2h later by 400 mg IV infusion over approximately 20 min. Eight blood samples were collected after oral administration and nine samples were collected after IV administration up to 48 h after the oral dose, or until discharge for obese participants. Blood samples were collected in heparin tubes, centrifuged at 1900 g for 5 min and stored at −80°C until analysis.

In all individuals, 24h urine and serum creatinine were collected on the day of study and glomerular filtration rate (GFR) was calculated[13]. Additionally, estimated GFR values were calculated using the four-variable Modification of Diet in Renal Disease (MDRD)[14], the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[15] and the conventional Cockcroft–Gault, either calculated with total bodyweight (TBW) or with lean bodyweight (LBW)[16,17]. MDRD and CKD-EPI were de-indexed for body surface area (BSA) by multiplying the conventional values (in mL/min/1.73 m^2) by BSA/1.73[18].

Analytical assay

Fluconazole plasma concentrations were measured by a validated assay using LC coupled with tandem MS. Plasma samples were treated with protein precipitation procedures. The lower limit of detection (LOD) was 0.005 mg/L and the lower limit of quantification (LLOQ) and upper limit of quantification were 0.25 and 30.2 mg/L, respectively. The intraday and interday variability were 2.8% and 1.5%, respectively. The assay was externally validated by an international proficiency testing programme[19,20].

Population pharmacokinetic model

The population pharmacokinetic model was developed using the non-linear mixed-effects modelling software NONMEM (version 7.3.0; ICON Development Solutions, Hanover, MD, USA) supported by Perl-speaks-NONMEM (version 4.2.0) with the Pirana interface (version 2.9.0; Certara USA, Inc., Princeton, USA)[21]. Data pre-processing and visualization were performed with R 4.0.3 and RStudio 1.3.959. The first-order conditional estimation method with interaction was used for all model runs.

For concentrations below the LOD (17 samples, 4.0%), half the LOD (0.0025 mg/L) was imputed. When consecutive samples were below the LOD during the absorption phase, only the last concentration was imputed and the first was omitted. Concentrations between LOD and LLOQ (six samples, 1.4%) were included in the analysis as reported by the lab.

Model development consisted of: (1) selection of the structural model, including disposition and absorption model structures; (2) selection of the statistical error model including inter-individual variability (IIV) and residual unexplained variability (RUV); and (3) covariates analysis. One- and two-compartment disposition models with linear elimination were tested. Tested approaches to describe oral absorption included first-order absorption (with and without absorption lag time), transit compartment models, mixed first-order and zero-order absorption and a Weibull function[22-25]. Since peak concentrations were not discernible within 2 h for most individuals, a simulation and re-estimation approach was performed to confirm the identifiability of F, which was then included with a logit function. Proportional, additive and combined additive and proportional error models were assessed for RUV. Covariance between model parameters was assessed and included in the model if correlation coefficients were >0.8.

Model selection was based on the difference in objective function value (OFV, −2 log-likelihood), on the relative standard error of parameter estimates being <50%, physiological plausibility of the parameter estimates, and basic goodness-of-fit (GOF) plots. Particular attention was paid to unbiased description in the oral absorption phase.

Potential covariates were selected based on correlations between empirical Bayes estimates and the covariates in the base model. Tested covariates include sex, age, obesity (as a binary factor), TBW, BMI, BSA, LBW, ideal bodyweight and adjusted bodyweight[26-28]. The equations for the calculation of the different body size measures can be found in Table S1. As fluconazole is mainly renally cleared, kidney function-related measures were tested as covariates on CL. Equations for the calculation of these kidney function indices can be found in Table S2. Continuous covariates were tested with linear and power functions centralized for a typical individual of 70 kg for TBW or the median value for the covariate in the dataset. Binary covariates were incorporated with a proportional relationship. Covariate analysis followed a forward inclusion and backward deletion step, with the inclusion criteria of an OFV difference of >3.84 and >6.64, respectively.

The final model was validated using a jackknife analysis and a normalized prediction distribution error (NPDE) analysis based on 1000 simulations. Parameter precision was assessed using the sampling importance resampling method[29].

Model-based dosing evaluation and optimization

Stochastic simulations using the final model were performed to illustrate the influence of covariates on fluconazole exposure, to evaluate the currently recommended dosing, and to provide guidance on optimized dosing. Male and female representatives with TBWs of 60, 100, 130 and 170 kg were simulated 1000 times with IIV to predict fluconazole concentration–time profiles and the AUC_{24h}.

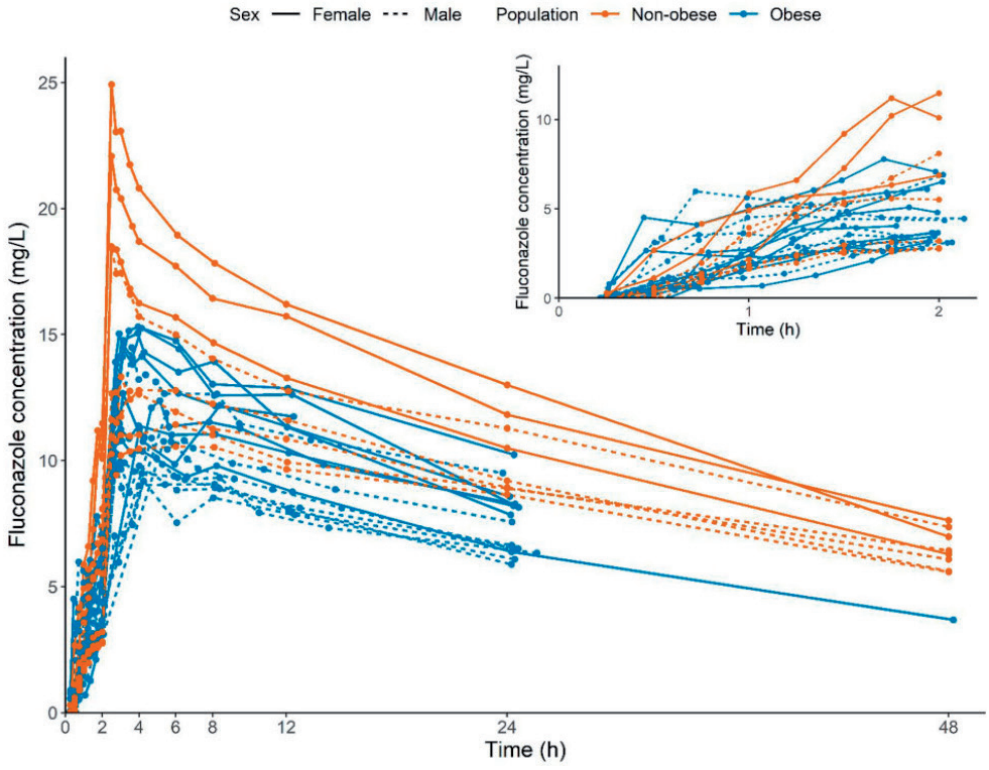
For the treatment of invasive fungal infections, a dose of 800 mg on Day 1 followed by a maintenance dose of 400 mg once daily was evaluated[30]. Other loading (Day 1)/maintenance oral dosing regimens that were evaluated included 400/200 or 200/100 mg, typically used for treating oropharyngeal or esophageal candidiasis, and 150 mg every third day for a total of three doses (Days 1, 4 and 7) in the first week, and 150 mg weekly for recurrent vaginal candidiasis[30,31]. An AUC_{24h} of >200 mg*h/L was selected as it is a target for the empirical treatment of invasive candidiasis that is not suspected to be located in the brain[10]. An AUC_{24h} of >400 mg*h/L was selected as it is a target for Candida meningitis or encephalitis[32-34]. AUC_{24h} on the first day of treatment and at steady state was used to assess the dosing regimen, aiming for >90% PTA. When PTA for the target of AUC_{24h} >400 mg*h/L was not achieved, higher doses up to 1600 mg daily were explored[35].

Results

Data

In total, 421 fluconazole concentrations from 25 Caucasian subjects (48% female), of which 17 were obese and 8 non-obese, with a TBW ranging from 61.0 to 174 kg, were included for pharmacokinetic analysis. One obese subject discontinued the study because of fluconazole extravasation during infusion (swelling disappeared within 24 h and no other abnormality was noted), whose concentrations measured upon oral dosing were included in the analysis. Subject details are presented in Table 1. All non-obese subjects and one obese subject had concentrations obtained until 48 h after the first dose; the remaining obese patients had observations up to 24 h. Figure 1 shows the obtained fluconazole concentration–time profiles.

Figure 1



Individual concentration–time profiles of fluconazole for non-obese healthy subjects (n=8, orange) and obese but otherwise healthy subjects (n=17, blue). The upper right insert zooms in on the concentration–time profile in the first 2 h after oral dosing before IV administration.

Population pharmacokinetic model

Three absorption transit compartments connected by a one-compartment disposition model with first-order elimination and a combined proportional and additive residual error model best described the data.22 Covariance values between parameters were all lower than 0.8. IIV was included on F, V_d and the first-order rate constant between absorption transit compartments. No statistically significant influence of obesity or body size descriptors were found on F, therefore in the final model, the same F of 87.5% was estimated for obese and non-obese groups. IIV was relatively high, described as a 95% distribution interval of 43.9%–98.4%. Parameter estimates of the final model are presented in Table 2.

Table 1: Patient and data characteristics of the obese and non-obese subjects included in the pharmacokinetic analysis

Characteristic	Obese	Non-obese
No of subjects	17	8
Sex, n (%)		
Male	8 (47)	5 (63)
Female	9 (53)	3 (37)
Demographics, median (range)		
Age, years	44 (25–62)	35 (23–60)
TBW, kg	148 (106–174)	77.2 (61.0–93.5)
BMI, kg/m^2	44.1 (37.6–57.2)	23.7 (19.0–26.9)
BSA, m^2	2.54 (2.11–2.82)	1.95 (1.69–2.19)
LBW, kg	75.0 (53.8–88.7)	60.0 (40.2–69.4)
Ideal bodyweight, kg	72.3 (55.1–83.1)	73.4 (58.7–81.3)
Adjusted bodyweight, kg	101 (76.6–114)	75.8 (60.2–85.9)
Renal function measures, median (range)		
CKD-EPI, mL/min/1.73 m^2	143 (108–175)	106 (83.1–145)
De-indexed CKD-EPI, mL/min[b]	94.9 (79.7–120)	94.5 (79.0–120)
MDRD, mL/min/1.73 m^2	133 (102–178)	101 (77.7–147)
De-indexed MDRD, mL/min[b]	94.0 (74.0–116)	90.0 (76.0–122)
Cockcroft–Gault with TBW, mL/min	222 (143–290)	108 (74.2–161)
Cockcroft–Gault with LBW, mL/min	105 (72.6–143)	76.1 (51.3–126)
Sampling profile		
No. of samples	277	144
No. of samples/subject, median (range)	16.3 (8–18)	18.0 (18–18)

[a] *GFR was calculated based on 24 h urine.*

[b] *De-indexed for BSA by multiplying the conventional values (in mL/min/1.73 m^2) by BSA/1.73.*

TBW in a power function in combination with sex presented a similar potential to describe IIV on V_d as LBW in a power function, yielding an OFV reduction of 45.1 versus 44.8 and a reduction of IIV on V_d from 25.2% to 6.80% versus 6.70%, respectively, with no discernible difference in GOF plots. The covariate function based on TBW and sex was included in the final model, as these are more readily available in clinical practice. Incorporating TBW on CL using a power function further improved the GOF plots and dropped the OFV by 17.7 points ($P<0.001$). Figure 2 illustrates the influence of TBW and sex on V_d, and TBW on CL from the final model. Introducing kidney function indices or other demographics did not further improve the model.

GOF plots indicate good descriptive performance of the final model and are presented in Figure S1. The jackknife results show that exclusion of none of the individuals caused

a >10% change in pharmacokinetic parameter estimates, indicating an absence of influential individuals. The NPDE results, shown in Figure S2, indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for obese and non-obese subjects.

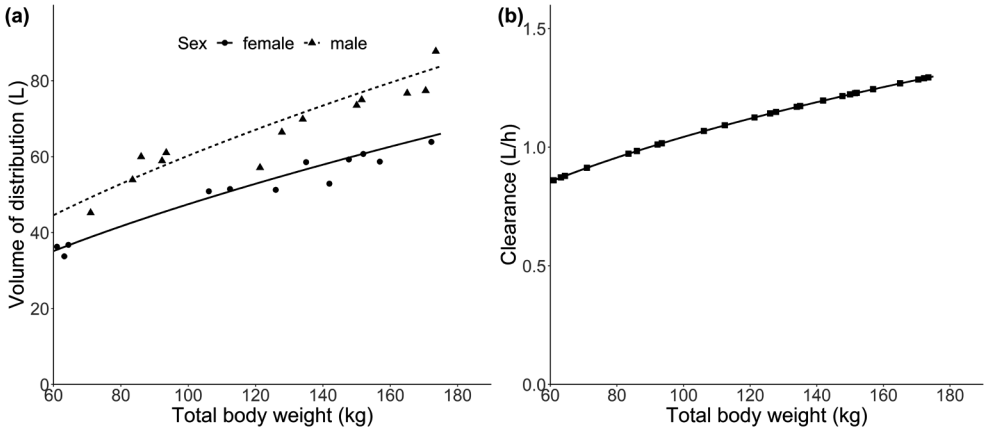
Table 2: Pharmacokinetic parameter estimates for the final model

Parameter	Estimated values (RSE %) [95% CI]
$F = \frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}\right)}}$	
θ_F (%)	87.5 (7.70) [77.9–96.2]
k_{tr} (h^{-1})	2.69 (10.5) [2.30–3.22]
$CL = CL_{70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,CL}}$	
$CL_{70\ kg}$ (L/h)	0.908 (3.00) [0.868–0.945]
$\theta_{TBW,CL}$	0.390 (20.4) [0.214–0.532]
$V_{d,female} = V_{d,70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,V_d}}$	
$V_{d,male} = V_{d,70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,V_d}} \times (1+\theta_{sex})$	
$V_{d,70\ kg}$ (L)	38.5 (2.50) [36.6–40.6]
θ_{TBW,V_d}	0.567 (10.6) [0.474–0.679]
θ_{sex}	0.269 (21.0) [0.177–0.364]
IIV in coefficient of variation (%) (RSE%)	
k_{tr}	45.9 (14.0) [32.9–57.9]
V_d	7.26 (23.8) [4.42–10.2]
θ_F[a]	158 (25.7) [79.9–320]
Residual error in variance (RSE%)	
σ_{prop}	0.0033 (33.0) [0.00163–0.00522]
σ_{addi} (mg/L)	0.266 (30.5) [0.180–0.397]

CL: Clearance obtained in the sampling importance resampling procedure, $CL_{70\ kg}$, the population mean value of CL for a subject with a weight of 70 kg, k_{tr}: first-order rate constant between absorption transit compartments, RSE: relative standard error, σ_{prop}: proportional residual error, σ_{addi}: additive residual error. θF: population mean value of F, θ_{sex}: proportional increase in V_d for male compared with female subjects, $\theta_{TBW,CL}$: exponent in the exponential covariate relationships between TBW and CL, $\theta_{TBW,Vd}$: exponent in the exponential covariate relationships between TBW and V_d, $V_{d,female}$: V_d for female subjects, $V_{d,male}$: V_d for male subjects, $V_{d,70\ kg}$: the population mean value of the V_d for a subject with a body weight of 70 kg.

[a] Due to logit transformation, IIV of F could be described as 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $(\frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}-1.96\times\sqrt{\omega_F{}^2}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}-1.96\times\sqrt{\omega_F{}^2}\right)}})$ and $(\frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}+1.96\times\sqrt{\omega_F{}^2}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}+1.96\times\sqrt{\omega_F{}^2}\right)}})$ i.e. 43.9% and 98.4%.

Figure 2



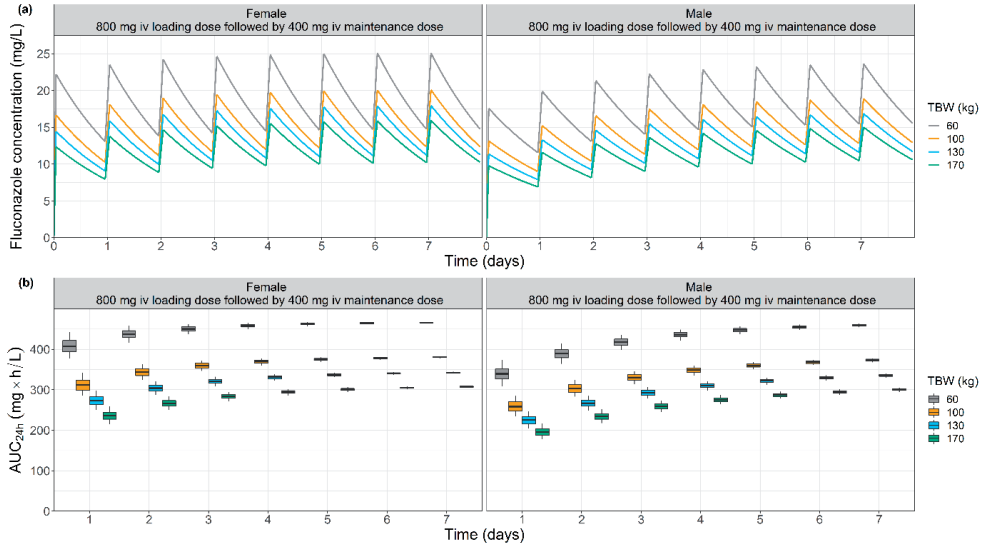
Individual empirical Bayes estimates (filled circles, filled triangles and filled squares) for the Vd (a) and CL (b) versus TBW from the final model. Lines represent the model-predicted relationships between the Vd and CL versus TBW.

Dose evaluations

Simulation results of the recommended fluconazole IV dosage regimen for invasive candidiasis in Figure 3 indicate that heavier subjects have lower steady-state exposure compared with lighter subjects. Moreover, male subjects have lower exposure early after treatment initiation compared with female subjects of the same weight and it takes longer for male and heavier subjects to reach steady state in comparison with female and lighter subjects. Figure 4 presents the distribution of fluconazole AUC_{24h} versus TBW on Day 1 and Day 7. With this regimen, all female subjects and 90% of male subjects lighter than 140 kg achieved the target of AUC_{24h}>200 mg*h/L on Day 1, and all individuals achieved this target at steady state. However, only subjects lighter than 80 kg obtained the target of AUC_{24h}>400 mg*h/L for the treatment of Candida meningitis or encephalitis at steady state.

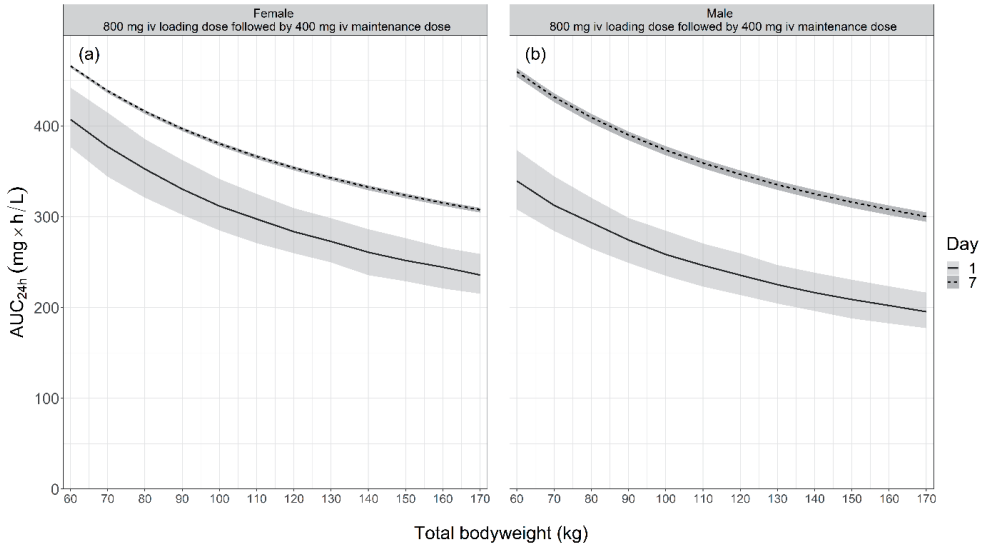
To ensure that all subjects receiving fluconazole IV achieve the target of AUC_{24h}>200 mg*h/L on the first day of treatment, male subjects heavier than 140 kg need a higher loading dose of 600 mg twice daily, compared with 800 mg once daily (Figure 5). To achieve an AUC_{24h}>400 mg*h/L at steady state, the fixed IV maintenance dose has to be increased from 400 to 600 mg per day for all patients (Figure S3). To achieve this high target on the first day, doses above 1600 mg, which are deemed potentially unsafe, are needed for most patients, particularly for male subjects (Figure S3).

Figure 3



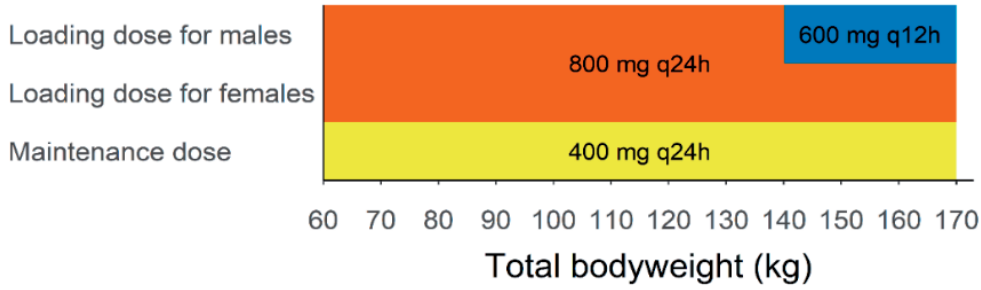
Median fluconazole concentration–time profiles (a) and distribution of the AUC24h (b) based on 1000 simulations of female and male subjects of various TBWs receiving a recommended IV loading dose of 800 mg once daily followed by a maintenance dose of 400 mg once daily. The boxes represent the 25th, 50th (median) and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval).

Figure 4



Distribution of AUC24h values versus TBW for fluconazole on Day 1 (solid line) and Day 7 (dashed line) based on 1000 simulations in female (a) and male (b) subjects receiving an IV loading dose of 800 mg once daily followed by a maintenance dose of 400 mg once daily. The shaded areas represent the 90% prediction interval.

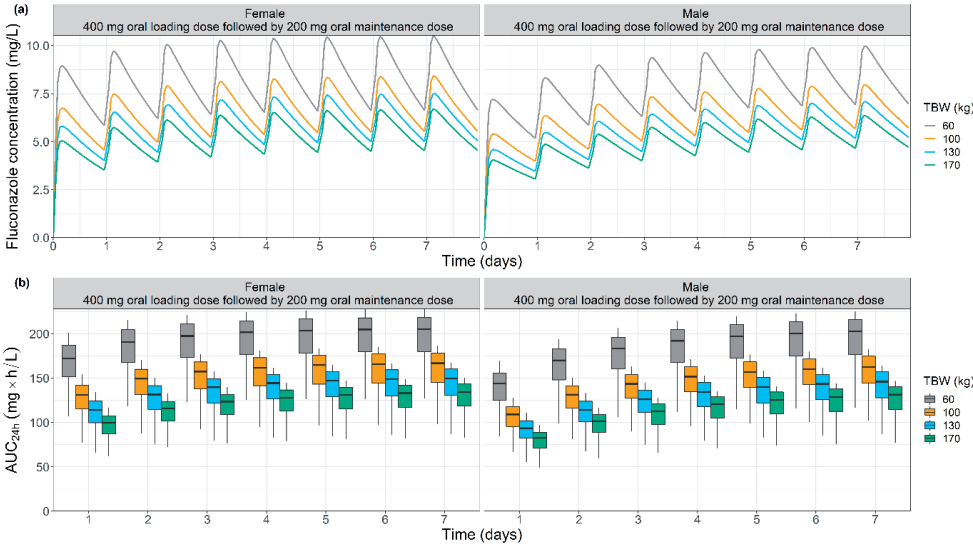
Figure 5



*Model-derived IV loading and maintenance dose recommendations for fluconazole for achieving a target AUC_{24h}>200 mg*h/L for the first day of treatment in female and male subjects of various TBWs.*

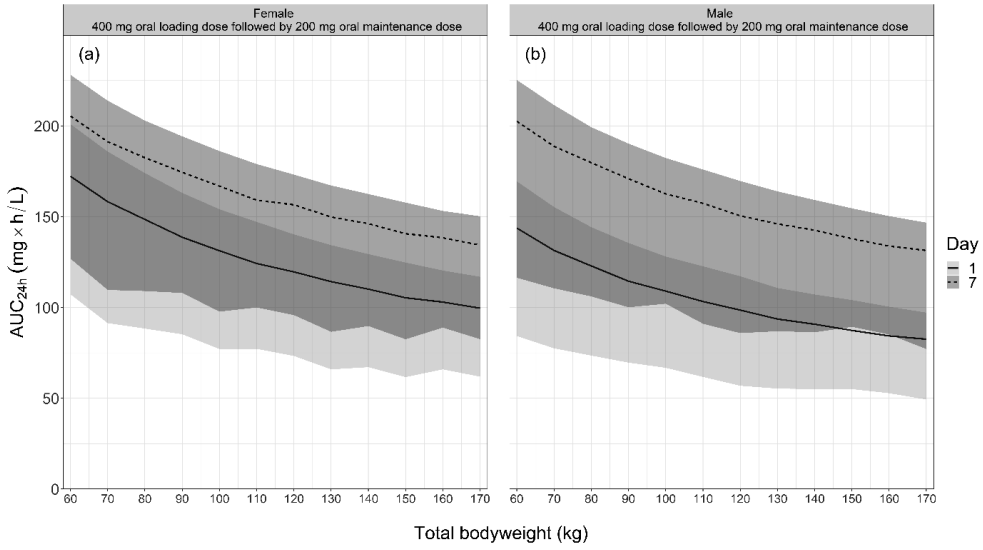
Figures 6 and 7 present simulation results for a commonly used oral dosing regimen prescribed for treating oropharyngeal or esophageal candidiasis. Due to the high IIV on F, exposure is highly variable for all weights. With the lower dose and variable F, no obese individual achieved the target of AUC_{24h}>200 mg*h/L. Other frequently used fluconazole oral dosing regimens were evaluated and the results can be found in Figures S4–S7.

Figure 6



Median fluconazole concentration–time profiles (a) and distribution of the AUC24h (b) based on 1000 simulations of female and male subjects of various TBW receiving a recommended oral loading dose of 400 mg once daily followed by a maintenance dose of 200 mg once daily. The boxes represent the 25th, 50th (median) and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval).

Figure 7



Distribution of AUC24h values versus TBW for fluconazole on Day 1 (solid line) and Day 7 (dashed line) based on 1000 simulations in female (a) and male (b) subjects receiving an oral loading dose of 400 mg once daily followed by a maintenance dose of 200 mg once daily. The shaded areas represent the 90% prediction interval.

Discussion

This study shows that obesity alters fluconazole pharmacokinetics. The typical F of fluconazole capsules (87.5%) is within the reported range of 78%–162%,[36] and no statistically significant difference was identified on the F or absorption rate constant between the obese and non-obese, indicating that obesity has a very limited influence on the rate and extent of absorption of fluconazole capsules. Despite a high average F for fluconazole capsules, caution should be taken when switching from IV to the oral capsule due to the high IIV in F. In obese adults up to 174 kg, TBW is significantly correlated with V_d and CL, which can be described with power function (Table 2). Additionally, the V_d in male subjects is on average 26.9% larger than in female subjects of the same weight.

Only a few studies investigated fluconazole in the obese population. Alobaid *et al.*[36]. investigated the pharmacokinetics of fluconazole in critically ill obese patients. Although no statistically significant covariate relationship was found from this study, the measured CL_{CR} was included as a covariate on CL, merely due to the improvement in the diagnostic plots and, similarly, BMI was used as a descriptor for V_d of the central compartment based on biological plausibility and improvement from the diagnostic

plots. The small sample size in this study and the pathophysiological complexity of critically ill patients might have obscured the impact of obesity. An important strength of our study is the prospective study design with semi-simultaneous oral and IV dosing, which allows for an accurate estimation of F by reducing the influence of inter-occasion variability, the intensive sampling and the wide range of TBW. By selecting relatively healthy individuals, the potentially confounding influence of pathological factors such as renal dysfunction is circumvented; however, this comes with the limitation that extrapolations to patients, particularly patients with renal dysfunction or other relevant pathological factors, cannot be made directly. Although the bariatric surgery during this pharmacokinetic study might interfere with the pharmacokinetics, we anticipate that this influence may be negligible as the duration of this surgery is short (<1 h) with minor blood loss (<50 mL). Although the population CL in the healthy obese patients from our study is very similar to what has been reported in critically ill obese patients (0.908 versus 0.950 L/h), a high IIV of 50.5% on CL was found in those patients while no IIV on CL could be identified by our model, which suggests it may be more challenging to dose critically ill obese patients with whom multiple comorbidities are commonly associated[37]. Pharmacokinetics studies conducted in various patient populations identified that kidney function and disease severity are associated with fluconazole CL[37–40]. We have not found kidney function estimates to be statistically significant predictors of IIV, which is likely attributable to the absence of individuals with impaired renal function. Additionally, in our model, the fluconazole CL of a 70 kg healthy individual is 0.908 L/h, corresponding to 15.1 mL/min, which is much lower than the average GFR in our population. This is in line with previous reports on extensive passive tubular reabsorption of fluconazole[41]. Although concentrations at 48 h were mostly missing from the obese group, no clear change in the elimination profile was noticed from 24 to 48 h based on the available concentrations at 48 h. Additionally, the estimation results of the final model remain similar when all concentrations at 48 h were excluded. Therefore, we do not expect that these missing observations at 48 h would alter our findings.

In addition to TBW, we found sex to be correlated with V_d. Interestingly, as sex is incorporated in the calculation of LBW, a similar descriptive potential of IIV in V_d could be obtained with LBW in comparison with the combination of TBW and sex. The contribution of height in the calculation of LBW appears to be negligible in our analysis, possibly because the range in height covers a difference of less than 30 cm. We decided to include the combination of TBW and sex to facilitate the clinical implementation of model-derived dosing recommendations by avoiding complex calculations of LBW. Higher body fat composition, namely a lower body water composition in female versus male subjects with the same TBW, could potentially explain the smaller V_d in female

subjects[42]. Due to the increased V_d, obese male subjects with TBW ≥140 kg need an increased loading dose (Figure 5) to achieve target exposure on the first day of treatment.

With the dosing recommendations for obese patients as derived in our study (Figure 5), the target of AUC_{24h}/MIC>100 for a pathogen with MIC≤2 mg/L can be achieved. This recommendation is anticipated to be safe as a 1200 mg daily dose for 2 weeks has shown good tolerance and no liver function disturbance in 30 HIV patients[43]. A recent pharmacokinetic study in critically ill obese patients suggested a TBW-based loading dose of 12 mg/kg and a maintenance dose of 6 mg/kg for pathogens with an MIC of 2 mg/L. With this dosing strategy, a loading dose of >1600 mg is required in patients with TBW>130 kg, which is partly unnecessary according to our simulation (Figure 5) and potentially unsafe.[35] For the empirical treatment of Candida meningitis or encephalitis, a higher exposure might be desirable to compensate for the 20%–50% reduced fluconazole penetration into the CSF[32,33]. Therefore we also assessed PTA for an AUC_{24h} target of 400 mg*h/L, and the simulation results indicate that an increased maintenance dose of 600 mg versus 400 mg once daily is required, and loading doses exceeding 1600 mg for female subjects ≥140 kg and male subjects ≥90 kg to meet this target on Day 1 (Figure S3)[35]. Clinicians should balance potential fluconazole-related toxicity with the decreased PTA when treating obese patients with Candida infections in the CNS.

We investigated the exposure levels for three commonly used fluconazole oral regimens including a loading (first day)/maintenance dose of 400/200 mg, 200/100 mg and 150 mg every third day for a total of three doses (Day 1, 4 and 7) in the first week, and 150 mg weekly (Figures 6–7 and Figures S4–S7), which are primary treatments for superficial and mucosal Candida infections. Hardly any individual with TBW between 80 and 170 kg reached the AUC_{24h}>200 mg*h/L target with these doses, yet favorable clinical responses have been reported, suggesting that a lower target exposure may be effective[44,45]. This could potentially be explained by the sufficient penetration of fluconazole[46]. Alternatively, the susceptibility of Candida spp. to fluconazole could be increased, or the immune response is more active with these infections. Symptomatic relapse of vulvovaginal candidiasis was reported in approximately 40% of women, while recurrent oropharyngeal and esophageal candidiasis have also become an increasingly prevalent clinical issue[31,44]. Potentially these refractory superficial infections might result from the highly variable F we observed in obese and non-obese individuals, which means that a certain proportion of patients can be underexposed because they have a low F that could even exacerbate the infection by selecting more resistant strains of Candida spp.

Conclusion

Our results show that in otherwise healthy obese adults, both fluconazole CL and V_d increase with increasing TBW, with sex being an additional covariate for the V_d, resulting in a larger V_d in male compared with female subjects of the same weight. As a result, male subjects with high TBW may need increased loading doses as the time to steady state is longer. Model-based evaluations of commonly used oral dosing regimens illustrate high variability in exposure due to the high IIV in F, which could put large proportions of obese individuals at higher risk of underexposure.

Acknowledgements and disclosures

We would like to thank all patients and volunteers who participated in this study. We would also like to thank Angela Colbers, Brigitte Bliemer and Sylvia Samsom for their help with the inclusion of participants.

No disclosures are applicable for this work. Disclosures outside of this work: R.J.B. and P.E.V. have served as consultants to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp. and Pfizer, Inc., and have received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp. and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors have any conflicts to declare.

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Supplementary material

Table S1: Equations used for calculating body size measures

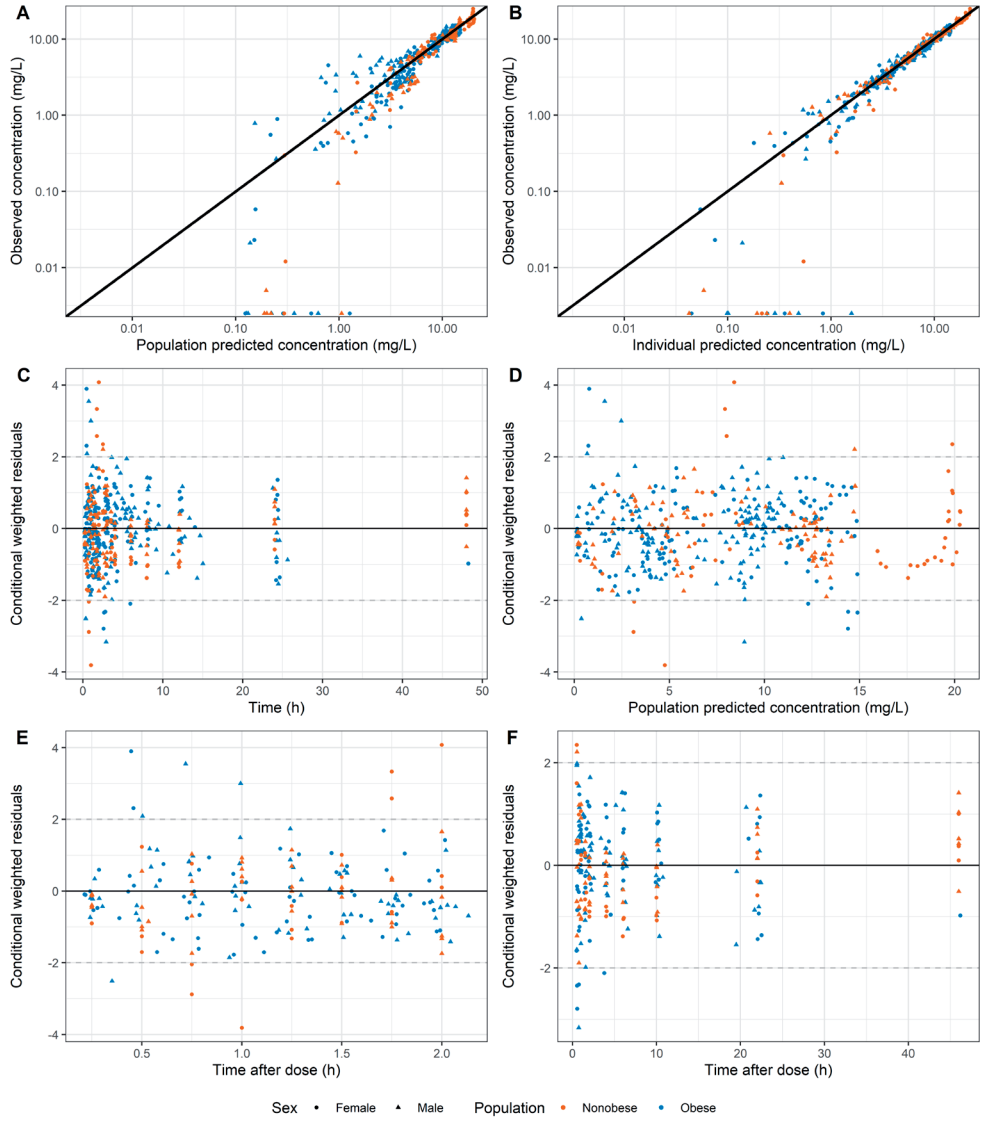
Body size measure	Equation	Reference
Body mass index (BMI), kg/m^2	$BMI = \frac{TBW(kg)}{Height(m)^2}$	
Body surface area (BSA), m^2	$BSA = TBW(kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$	1
Lean bodyweight (LBW), kg	$LBW_{male} = \frac{9270 \times TBW}{6680\ +\ 216\ \times\ \mathrm{BMI}}$	2
	$LBW_{female} = \frac{9270 \times TBW}{8780\ +\ 244\ \times\ \mathrm{BMI}}$	
Ideal bodyweight (IBW), kg	$IBW_{male} = 50 + 2.3 \times (Height(\mathrm{cm}) \times 0.3937 - 60)$	3
	$IBW_{female} = 45.5 + 2.3 \times (Height(\mathrm{cm}) \times 0.3937 - 60)$	
Adjusted bodyweight (ABW), kg	If TBW ≥ IBW, ABW = IBW + 0.4 × (TBW - IBW) If TBW < IBW, ABW = IBW	3
	If TBW ≥ IBW, ABW = IBW + 0.4 (TBW - IBW) If TBW < IBW, ABW = IBW	

Table S2: Equations used for calculating renal function indices.

Renal function index	Equation	Ref
Glomerular filtration rate (GFR), mL/min	$\text{GFR} = \frac{Ucr(\mu mol/L)}{Scr(\mu mol/L)} \times \frac{urine\ volume\ (mL)}{collection\ time\ (min)}$	4
Chronic Kidney Disease Epidemiology (CKD - EPI) mL/min/1.73 m^2	$\text{CKD-EPI}_{male,\ nonblack} = 141 \times \min\left(\frac{Scr(mg/dL)}{0.9}, 1\right)^{-0.411} \times \max\left(\frac{Scr(mg/dL)}{0.9}, 1\right)^{-1.209} \times 0.993^{AGE}$	5
	$\text{CKD-EPI}_{female,\ nonblack} = 141 \times \min\left(\frac{Scr(mg/dL)}{0.7}, 1\right)^{-0.329} \times \max\left(\frac{Scr(mg/dL)}{0.7}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.018$	
	$\text{CKD-EPI}_{male,\ black} = 141 \times \min\left(\frac{Scr(mg/dL)}{0.9}, 1\right)^{-0.411} \times \max\left(\frac{Scr(mg/dL)}{0.9}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.159$	
	$\text{CKD-EPI}_{female,\ black} = 141 \times \min\left(\frac{Scr(mg/dL)}{0.7}, 1\right)^{-0.329} \times \max\left(\frac{Scr(mg/dL)}{0.7}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.018 \times 1.159$	
De-indexed CKD-EPI, mL/min	$\text{De-indexed CKD-EPI} = \frac{\text{CKD-EPI} \times BSA(m^2)}{1.73}$	
Modification of Diet in Renal Disease (MDRD), mL/min/1.73 m^2	$\text{MDRD}_{male,\ nonblack} = 175 \times (Scr(mg/dL))^{-1.154} \times AGE(years)^{-0.203}$	6
	$\text{MDRD}_{female,\ nonblack} = 175 \times (Scr(mg/dL))^{-1.154} \times AGE(years)^{-0.203} \times 0.742$	
	$\text{MDRD}_{male,\ black} = 175 \times (Scr(mg/dL))^{-1.154} \times AGE(years)^{-0.203} \times 1.212$	
	$\text{MDRD}_{female,\ black} = 175 \times (Scr(mg/dL))^{-1.154} \times AGE(years)^{-0.203} \times 0.742 \times 1.212$	
De-indexed MDRD, mL/min	$\text{MDRD-di} = \frac{\text{MDRD} \times BSA(m^2)}{1.73}$	
Cockcroft-Gault with TBW, mL/min	$\text{CG}_{TBW\ male} = \frac{(140 - age(years)) \times TBW(kg)}{72 \times Scr(mg/dL)}$	7
	$\text{CG}_{TBWfemale} = \frac{(140 - age(years)) \times TBW(kg)}{72 \times Scr(mg/dL)} \times 0.85$	
Cockcroft-Gault with LBW, mL/min	$\text{CG}_{LBWmale} = \frac{(140 - age(years)) \times LBW(kg)}{72 \times Scr(mg/dL)}$	8
	$\text{CG}_{LBWfemale} = \frac{(140 - age(years)) \times LBW(kg)}{72 \times Scr(mg/dL)} \times 0.85$	

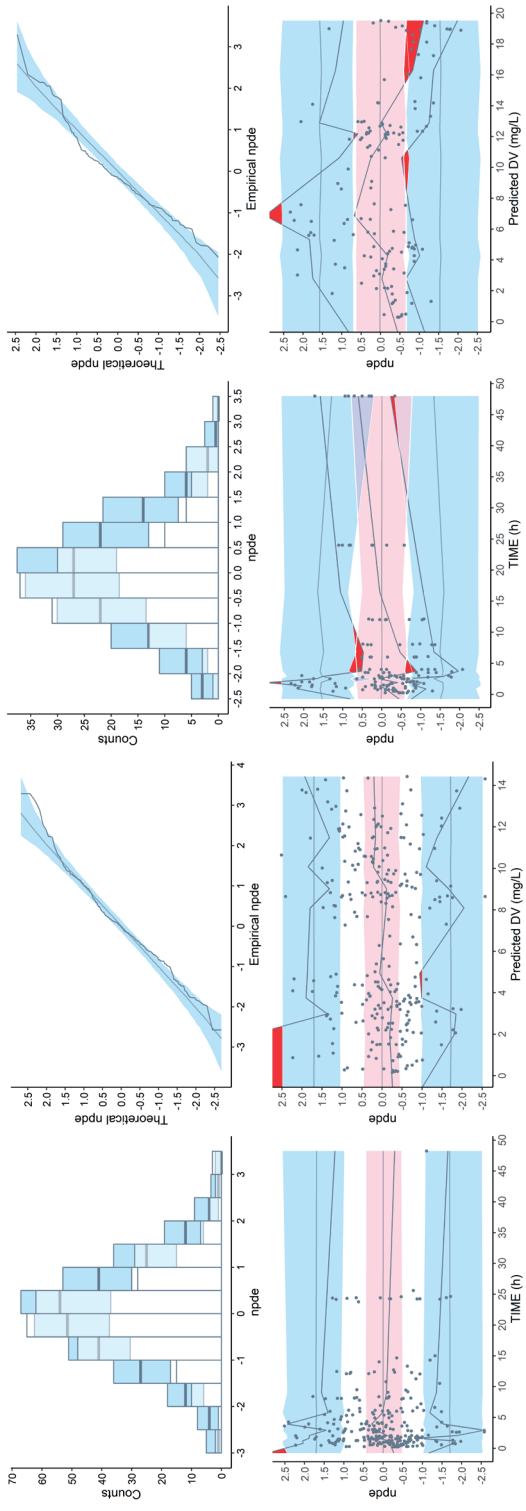
Ucr urine creatinine, Scr serum creatinine

Figure S1



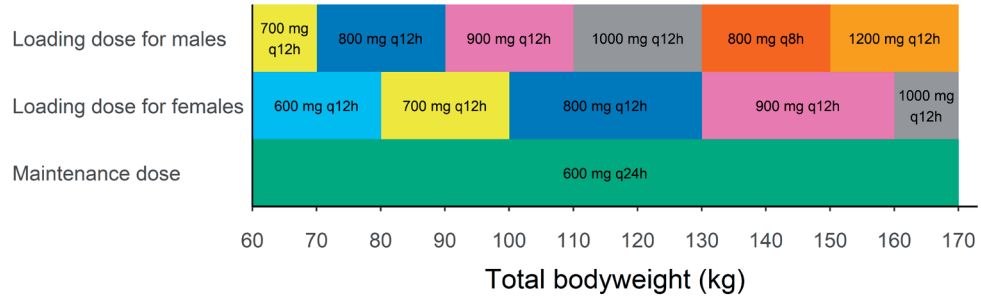
Goodness-of-fit plots of the final population pharmacokinetic model of fluconazole:
a *observed versus population predicted fluconazole concentrations*
b *observed versus individual predicted fluconazole concentrations*
c *conditional weighted residuals versus time after first (oral) fluconazole administration*
d *conditional weighted residuals versus population predicted fluconazole concentrations*
e *conditional weighted residuals versus time after dose for observations after the oral dose only*
f *conditional weighted residuals versus time after dose for observation after the iv infusion*

Figure S2



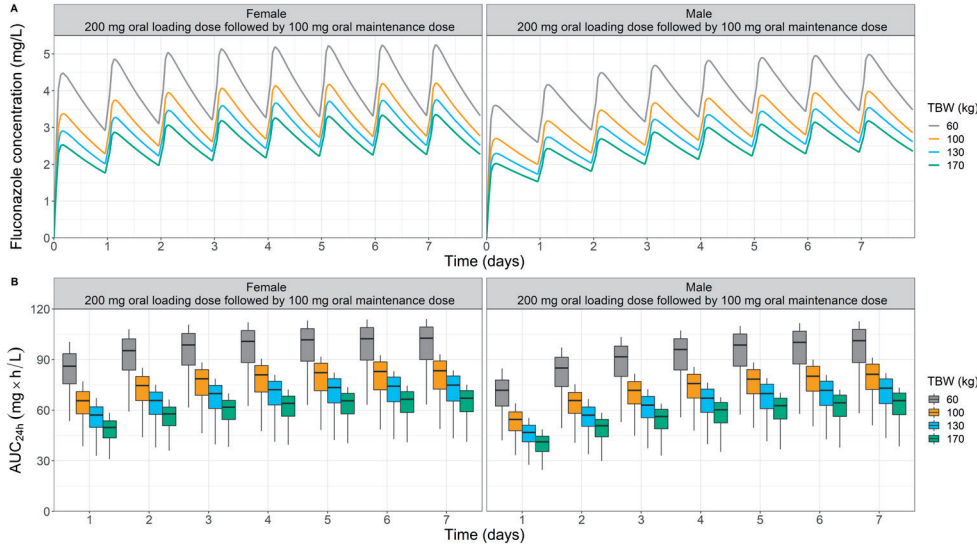
Normalized prediction distribution error (NPDE) results of the final model (n = 1000) stratified for obese (A) and non-obese (B) subjects. In plots of NPDE versus Time and NPDE versus Predicted DV, each prediction interval (95%) is plotted as a colored area (blue for the 2.5 and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed data are plotted as jagged lines. The outliers of the bounds of the confidence interval are highlighted in red.

Figure S3



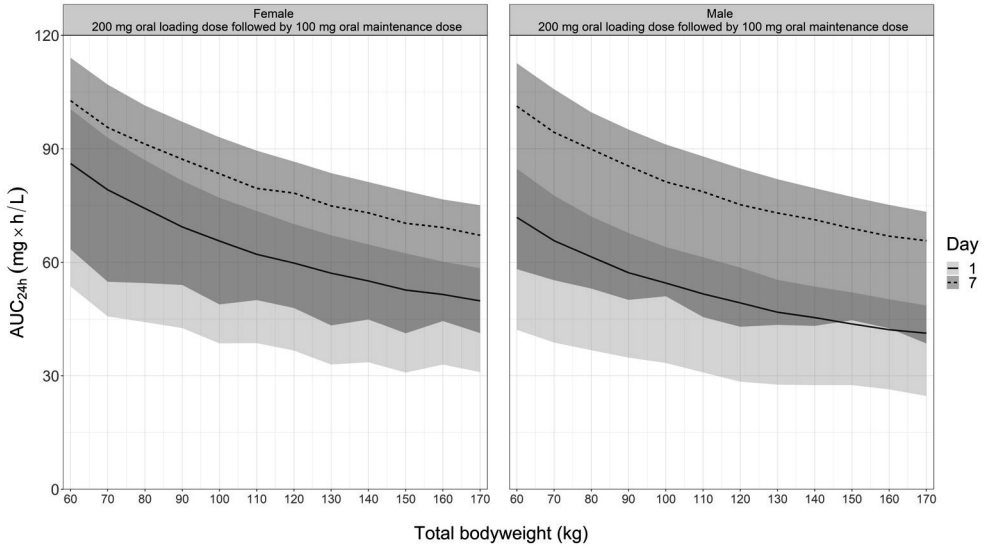
*Simulation-based iv loading dose and maintenance dose of fluconazole for achieving the target of AUC_{24h} > 400 mg*h/L in female and male subjects of various total bodyweight. Target attainment for fluconazole loading dose and maintenance dose was assessed on day 1 and day 7, respectively. A total daily dose of up to 1600 mg was reported to be well tolerated in patients, above which neurological toxicity was observed[9]. q24h: dose every 24 h, q12h: dose every 12h, q8h: dose every 8h.*

Figure S4



Median fluconazole concentration-time profiles (A) and distribution of the area under the curve per day (AUC_{24h}) (B) based on 1000 simulations of female and male subjects of various total bodyweight (TBW) receiving a recommended oral loading dose of 200 mg once daily followed by a maintenance dose of 100 mg once daily. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval). This dosage yields half of the exposure compared with the 400-200 mg regimen as presented in Figure 6.
Note: the scale on the y-axis is different from the scales of the figures in the main text.

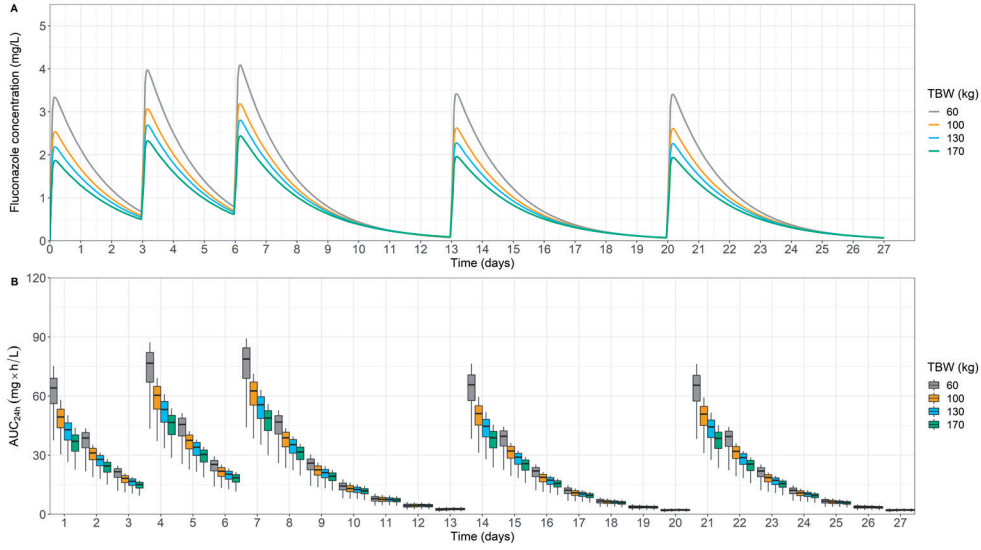
Figure S5



Distribution of AUC_{24h} values versus total bodyweight (TBW) for fluconazole on day 1 (solid line) and day 7 (dashed line) based on 1000 simulations in female (left) and male (right) subjects receiving an oral loading dose of 200 mg once daily followed by a maintenance dose of 100 mg once daily. The shaded areas represent the 90% prediction interval. This dosage yields half of the exposure compared with the 400-200 mg regimen as presented in Figure 7.

Note: the scale on the y-axis is different from the scales of the figures in the main text.

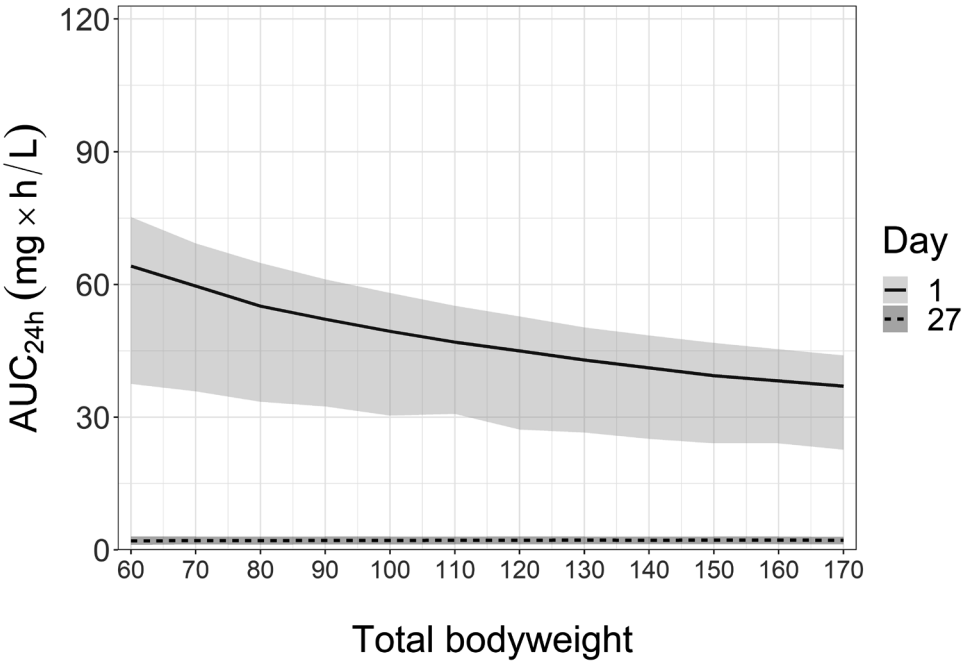
Figure S6



*Median fluconazole concentration-time profiles (A) and distribution of the area under the curve per 24-h (AUC_{24h}) (B) based on 1000 simulations of female subjects of various total bodyweight (TBW) receiving an oral loading dose of 150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by a maintenance dose of 150 mg once weekly for treating recurrent vaginal candidiasis for 28 days. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval). The simulation results showed that the average maximum concentrations (C_{max}) for all individuals are below 5 mg/L and the corresponding AUC_{24h} is less than 100 mg*h/L.*

Note: the scale on the y-axis is different from the scales of the figures in the main text.

Figure S7



Distribution of AUC_{24h} values versus total bodyweight (TBW) for fluconazole on day 1 (solid line) and day 27 (dashed line) based on 1000 simulations in female subjects receiving an oral loading dose of 150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by a maintenance dose of 150 mg once weekly for treating recurrent vaginal candidiasis for 28 days. The shaded areas represent the 90% prediction interval.

Note: the scale on the y-axis is different from the scales of the figures in the main text.

NONMEM Control Stream for the Final Model

```
$PROBLEM Fluconazole PK in obese and non-obese
$INPUT ID TIME AMT RATE DV LNDV MDV EVID CMT TAD OBESE ORAL IVDURA RATE1
DOSETIME PKNO IDORAL IDPK SEX AGE WT HT BMI BSA LBW IBW ABW OBESEHIS
OBESEAGE HEMT0 CREAT0 TBIL0 ALP0 ALT0 AST0 GGT0 URCREAT CKD0 CKDdi0 MDRD0
MDRDdi0 CGTBW0 CGLBW0 GFR
$DATA data.csv IGNORE=@
$SUB ADVAN13 TOL=9
$MODEL
COMP=(DEPOT)
COMP=(CENTRAL)
COMP=(TRANS1)
COMP=(TRANS2)

$PK
KTR = THETA(1)*EXP(ETA(1))
TVV2 = THETA(2)*(WT/70)**THETA(5)*(1+THETA(6)*SEX)
V2 = TVV2*EXP(ETA(2))
TVCL = THETA(3)*(WT/70)**THETA(7)
CL = TVCL*EXP(ETA(3))
TVF = THETA(4)
LGTBIO=LOG(TVF/(1-TVF))
LGBIO=LGTBIO+ETA(4)
F1= EXP(LGBIO)/(1+EXP(LGBIO))
K10 = CL/V2
S2 = V2

$DES
DADT(1)= -KTR*A(1)
DADT(2)= KTR*A(4) - K10*A(2)
DADT(3)= KTR*A(1) - KTR*A(3)
DADT(4)= KTR*A(3) - KTR*A(4)

$ERROR
IPRED = F
Y = IPRED * (1 + EPS(1)) + EPS(2)

$THETA
(0, 2.69) ; 1 KA
```

(0, 38.5) ; 2 V2
(0, 0.908) ; 3 CL
(0, 0.875,1) ; 4 F1
(0, 0.567) ; 5 WT/70 power on V2
(-1, 0.269) ; 6 SEX on V2
(0, 0.39) ; 7 WT/70 power on CL

$OMEGA
0.192 ; 1 KA
0.00526 ; 2 V2
0 FIX ; 3 CL
1.25 ; 4 F1

$SIGMA
0.0033 ; Proportional
0.266 ; Additive 0.1 ; Additive

$EST PRINT=5 MAX=9999 METHOD=1 NSIG=3 SIGL=6 INTERACTION POSTHOC NOABORT MSFO=mfi
$COV PRINT=E
$TABLE ID TIME AMT RATE DV LNDV MDV EVID CMT TAD OBESE ORAL IVDURA RATE1 DOSETIME PKNO IDORAL IDPK SEX AGE WT HT BMI BSA LBW IBW ABW OBESEHIS OBESEAGE HEMT0 CREAT0 TBIL0 ALP0 ALT0 AST0 GGT0 URCREAT CKD0 CKDdi0 MDRD0 MDRDdi0 CGTBW0 CGLBW0 GFR LLOQ KTR V2 CL F1 ETAS(1:LAST) IPRED PRED CWRES NOAPPEND NOPRINT ONEHEADER

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9. Anaissie EJ, Kontoyiannis DP, Huls C et al. Safety, plasma concentrations, and efficacy of high-dose fluconazole in invasive mold infections. J. Infect. Dis. 1995; 172: 599-602.

CHAPTER 3

3

Ciprofloxacin Pharmacokinetics After Oral and Intravenous Administration in (Morbidly) Obese and Non-obese Individuals: A Prospective Clinical Study

Koen P. van Rhee, Cornelis Smit, Roeland E. Wasmann,
Paul D. van der Linden, Rene Wiezer, Eric P.A. van Dongen,
Elke H.J. Krekels, Roger J.M. Brüggemann, Catherijne A.J. Knibbe



Abstract

Objective: Ciprofloxacin is a fluoroquinolone used for empirical and targeted therapy of a wide variety of infections. Despite the increase in obesity prevalence, there is only very limited guidance on whether the ciprofloxacin dose needs to be adjusted when given orally or intravenously in (morbidly) obese individuals. Our objective was to evaluate the influence of (morbid) obesity on ciprofloxacin pharmacokinetics after both oral and intravenous administration, ultimately to guide dosing in this population.

Methods: (Morbidly) obese individuals undergoing bariatric surgery received ciprofloxacin either orally 500mg (n=10) or intravenously 400mg (n=10). Non-obese participants received semi-simultaneous oral dosing of 500mg followed by intravenous 400mg three hours later (n=8). All participants underwent rich sampling (11-17 samples) for 12 hours after administration. Non-linear mixed effects modelling and simulations were performed to evaluate ciprofloxacin exposure in plasma. Subsequently, prior data from literature were included in the model to explore exposure in soft tissue in obese and non-obese patients.

Results: 28 participants with body weight ranging from 57–212kg were recruited. No significant influence of body weight on bioavailability, clearance or volume of distribution could be identified (all $p>0.05$). Soft tissue concentrations were predicted to be lower in obese individuals despite similar plasma concentrations compared to non-obese individuals.

Conclusion: Based on plasma pharmacokinetics we found no evidence of an influence of obesity on ciprofloxacin pharmacokinetic parameters. Therefore ciprofloxacin dosages do not need to be increased routinely in obese individuals. In case of treatment of infections in tissue where impaired ciprofloxacin penetration is anticipated, higher dosages may be required.

Introduction

Ciprofloxacin is a fluoroquinolone predominantly used for empirical and targeted treatment of urinary tract, complicated intra-abdominal, or lower respiratory tract infections[1]. In clinical practice, ciprofloxacin is often dosed two or three times daily, depending on the severity of infection and the pathogen[2]. Oral absorption of ciprofloxacin is mediated by organic anion transporting polypeptide (OATP) with a bioavailability of 56-77%[3,4]. Ciprofloxacin is subject to renal clearance by glomerular filtration, tubular secretion, hepatic clearance and trans-epithelial intestinal elimination[5].

Morbid obesity is defined as a body mass index (BMI) ≥40 kg/m^2 and can have a profound influence on absorption, distribution and clearance. The extent of this influence depends on drug properties like route of elimination, hepatic extraction ratio, involvement of transporters, protein binding, ionization and blood-plasma ratio[6,7]. While obesity showed no influence on OATP activity in obese overfed rats, it is unknown whether ciprofloxacin oral bioavailability is influenced by obesity in humans. Regarding clearance and volume of distribution conflicting results have been reported after intravenous ciprofloxacin administration in obese patients[8,9]. Clearance was unaltered by obesity in one study in which a relatively short sampling scheme after dosing was applied, complicating the identification of the influence of obesity on clearance[8]. Another study in less severely obese participants reported both an increased clearance and increased volume of distribution in obese patients[9]. Next to possible alterations in clearance from plasma and volume of distribution, obese patients showed a reduced penetration in soft tissue. More specifically, the mean penetration ratio from plasma to skeletal muscle was 0.82 for non-obese versus 0.45 for obese and 0.85 for non-obese versus 0.46 in obese for adipose tissue although the difference in penetration ratio in adipose tissue did not reach statistical significance[8].

To date, it is unclear how to dose ciprofloxacin in obese patients when given orally or intravenously. We report the results of a prospective rich sampling pharmacokinetic study in (morbidly) obese and non-obese participants in order to evaluate the impact of weight on ciprofloxacin pharmacokinetics after oral and intravenous administration. Additionally, soft-tissue penetration of ciprofloxacin as reported before was included in our population pharmacokinetic model to explore exposure in both plasma and soft tissue in obese and non-obese patients under commonly applied doses to derive dosing recommendations.

Materials and Methods

Participants

Eight healthy (BMI <25kg/m^2) and 20 (morbidly) obese individuals (BMI ≥40kg/m^2 or BMI ≥35kg/m^2 with co-morbidities) scheduled for bariatric surgery were eligible for inclusion. Exclusion criteria included: known hypersensitivity to ciprofloxacin, use of concomitant medication possibly interacting with ciprofloxacin clearance or absorption (e.g. CYP3A4 or CYP1A2 substrates, bivalent cations, opioids, proton-pump inhibitors, H_2-receptor antagonists, metoclopramide, erythromycin), a known prolonged QT-interval, known liver disease, pregnancy or breastfeeding, epilepsy, myasthenia gravis, or a known history of psychosis. This prospective study was performed at St. Antonius Hospital, Utrecht and Radboud university medical center in Nijmegen, The Netherlands. The study was approved by the local medical ethical review board, registered in the Dutch Trial Registry (NTR6058) and conducted in accordance with the principles of the declaration of Helsinki. All participants provided written informed consent before inclusion.

Study procedures

Obese individuals received a single dose of either 500mg oral or 400mg intravenous ciprofloxacin. Obese patients were assigned intravenous (IV) or oral (PO) ciprofloxacin at the researchers' discretion to ensure appropriate distribution of total body weight (TBW) within the respective subgroup. The oral dose was administered at least 3 hours before surgery to allow for complete absorption. A full concentration-time curve containing 11 (IV) or 15 (PO) samples per individual was collected over a 12-hour period after administration.

Non-obese participants received 500mg PO followed by 400mg IV infused over one hour, starting three hours after the oral dose. For non-obese participants, 17 samples (8 after PO and 9 after IV administration) were collected over 16 hours beginning after oral administration (see Online Resource for sampling scheme).

Samples were collected in EDTA-tubes, stored on ice, centrifuged at 1900g for five minutes and stored at -80°C until analysis. Total ciprofloxacin concentrations were analyzed using a validated ultra-performance liquid chromatography-tandem mass-spectrometric assay (Waters Brands, Milford, United States) with a concentration range of 0.050 to 10 mg/L. The low-level (0.050 mg/L) and high-level (10mg/L) within-day coefficients of variation (%CV) were 3.49% and 3.50%, respectively. The corresponding between day %CV were 3.21% and 2.46%, respectively.

For each participant data on weight, height, age, sex, duration and history of obesity were recorded. Serum creatinine was measured and 24-hour urine was collected during

the day of study to calculate the measured glomerular filtration rate (mGFR). Serum creatinine-based estimations of GFR were obtained using CKD-EPI (chronic kidney disease epidemiology collaboration[10]) and CKD-EPI$_{de\text{-}indexed}$ (de-indexed for body surface area (BSA) by multiplying CKD-EPI with BSA/1.73), MDRD (modifications of diet in renal disease[11]) and MDRD$_{de\text{-}indexed}$ (de-indexed for BSA), Cockroft-Gault (CG; based on total body weight and lean-body weight (LBW) for obese individuals; calculated using the Janmahasatian formula[12]), for non-obese patients TBW was used to calculate CG[13]. BSA was calculated using the Du Bois-Du Bois formula[14].

Pharmacokinetic analysis

All concentration-time data was analyzed by non-linear mixed-effects modelling (NONMEM; v7.4.0 with PsN; v4.7.1 and Pirana v2.9.7)[15-17]. Model building consisted of developing a structural, statistical and covariate model.

In NONMEM, the first-order conditional estimation method with interaction was used for all model runs. For the structural model, a transit compartment model and lag-time model were tested to describe oral absorption[18]. A one- and two-compartment model with first order elimination were tested to describe ciprofloxacin distribution. Log-normal distribution of inter-individual variability was assumed. Proportional, additive and combined residual error models were evaluated. A p-value of <0.05 —representing a 3.84 decrease in objective value function (OFV) for 1 degree of freedom— was considered statistically significant[15].

In the covariate-analysis, the influence of TBW, LBW, ideal body weight (IBW), BMI, sex, age, mGFR, MDRD, MDRD$_{de\text{-}indexed}$, CKD-EPI, CKD-EPI$_{de\text{-}indexed}$, and CGTBW CGLBW was tested on all pharmacokinetic parameters. Covariates were evaluated by forward inclusion ($p<0.05$; OFV decrease >3.84 for one degree of freedom) and backward deletion ($p<0.001$; OFV increase >10.8 for one degree of freedom), reduction in inter individual variability, evaluation of goodness-of-fit (GOF) plots, and Empirical Bayesian Estimate versus potential covariates. Internal model validation was done using visual predictive check (VPC). Model robustness and parameter precision were assessed using sampling-importance-resampling using 5000 samples and 1000 resamples[19]. For further details on the model building, see Online Resource.

After developing the structural, statistical and covariate model, the final model in plasma was extended with an additional compartment to allow for exploration of ciprofloxacin pharmacokinetics in tissue in obese and non-obese individuals. To this end, soft tissue concentration data from obese and non-obese patients were taken from literature through plot digitization[8]. Parameters describing transport to and elimination from the soft tissue were estimated as described in the Online Resource.

To develop guidance on dosing, the extended plasma and tissue model was used to explore concentration-time curves and exposure, reported as area under the curve (AUC), in both plasma and soft tissue after dosing regimens of a 2-4 times daily IV infusion of 400mg ciprofloxacin.

Results

Patients and data

Twenty (morbidly) obese participants with median (IQR) body weight of 141 (42) kg and median (IQR) mGFR of 148 (62) ml/min, and 8 healthy individuals with body weight of median (IQR) 66 (14) kg and median (IQR) mGFR 129 (17) ml/min were included. Details are described in Table 1. A total of 392 plasma samples were obtained, 1 sample (0.26%) was below the quantification limit at 30 minutes after oral administration and was excluded from analysis.

Table 1: Patient demographics

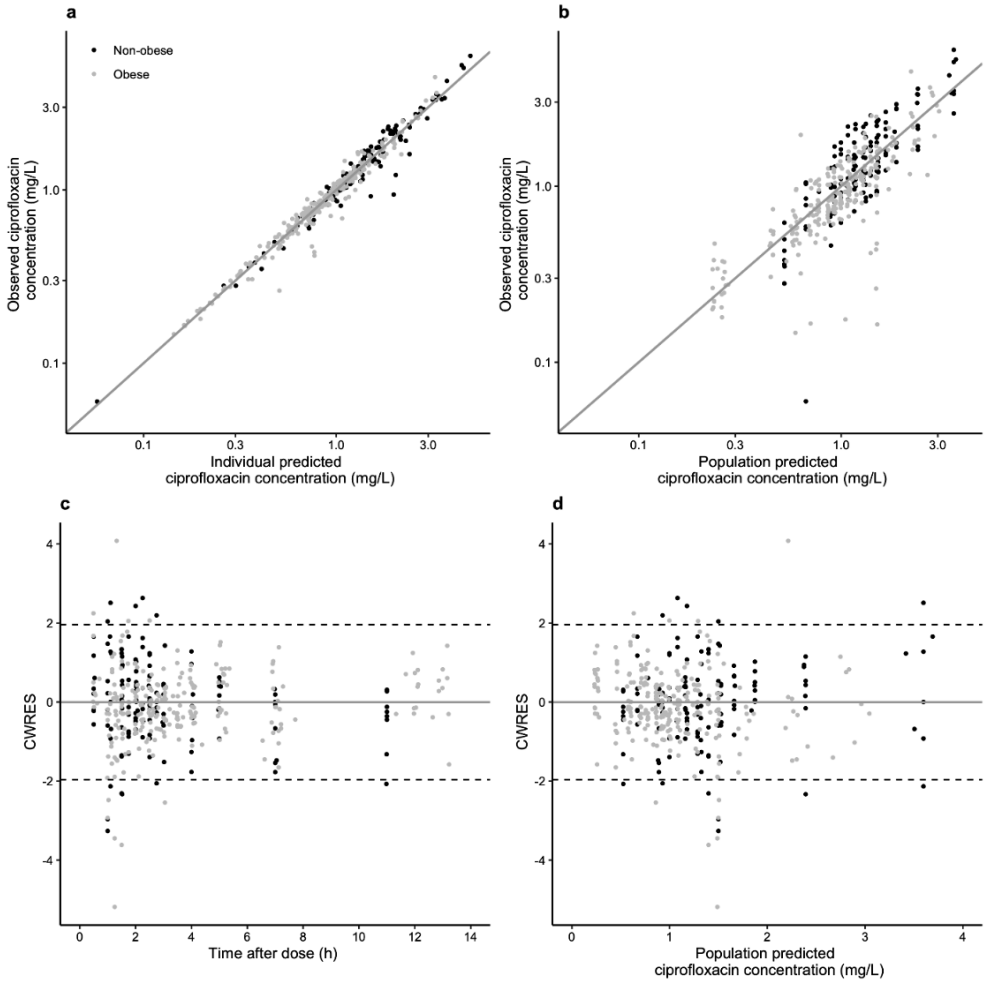
	Morbidly Obese (n=20)	Non-obese (n=8)
Total body weight (kg)	141 (42) [107-212]	66 (14) [57 – 85]
Lean body weight (kg)	70 (18) [52-102]	49 (20) [38-66]
BMI (kg/m^2)	45 (8.3) [39-58]	21 (4.2) [19-25]
Male sex (%)	50	50
Age (years)	49 (18) [27 – 59]	25 (3) [20 – 51]
Race (n)	Kaukasian 19 Asian 1	Kaukasian 8
mGFR 24h urine (ml/min)	148 (62) [100-254]	129 (17) [99-208]
Indexed CKD-EPI (ml/min/1.73m^2)	100 (18) [72-119]	107 (8) [84-118]
De-indexed CKD-EPI (ml/min)*	140 (29) [86-209]	113 (21) [80-139]
Indexed MDRD (ml/min/1.73m^2)	93 (21) [65-133]	92 (6) [74-103]
De-indexed MDRD (ml/min)*	133 (37) [78-221]	98 (21) [71-121]
Cockcroft-Gault with TBW (ml/min)	204 (53) [117-385]	110 (14) [74-144]
Cockcroft-Gault with LBW (ml/min)	105 (38) [57-200]	n.a.

BMI: Body mass index, mGFR: Measured glomerular filtration rate, TBW: Total body weight, LBW: Lean body weight[12]. Values are presented as median (IQR) [range] unless specified otherwise.
**De-indexing was done by multiplying the original CKD-EPI or MDRD by Body surface area /1.73*

Pharmacokinetic model

The observed data was best described using a two-compartment model with first-order elimination, inter-individual variability on clearance, central- and peripheral volume of distribution, intercompartmental clearance and a proportional error model.

Figure 1



Diagnostic plots of the final model for morbidly obese individuals (grey dots) and non-obese individuals (black dots). Observed versus individual predicted ciprofloxacin concentrations (a). Observed versus population predicted ciprofloxacin concentrations (b). Conditional weighted residuals versus (CWRES) time after dose (c). Conditional weighted residuals versus population predicted concentration (d).
The grey line represents the line of identity. The dashed lines represent the 1.96, -1.96 interval indicating the range within 95% of the observations are expected to fall.

Oral absorption was best described by a transit compartment model with covariance between bioavailability and mean-transit-time.

Body weight had no significant influence on bioavailability and oral absorption parameters, clearance or volume of distribution. Volume of distribution showed a trend with TBW, but this influence did not reach statistical significance (p>0.01, dOFV 6.2).

In the model with TBW as a covariate on CL an exponent of only -0.06 (RSE 194%) was found without an improvement of fit (p>0.05, dOFV -0.3)(see Figure S1). The final model adequately describes the observed data as is illustrated by Figure 1. The conditional weighted residuals indicate no model misspecification as distribution of residuals is homogenous over time and concentration (For VPC see figure S2). Parameter estimates of the final model are shown in Table 2.

Table 2: Parameters of the pharmacokinetic model

Parameter	Final model (%RSE)	SIR median [95%CI] 5000 samples/ 1000 resamples
Fixed effects		
CL (L/h)	31.7 (5.9)	32.1 [29.1-35.0]
V_c (L)	55.4 (16.8)	56.9 [39.9-72.5]
V_p (L)	144 (8.3)	146 [125-166]
Q (L/h)	87.8 (8.1)	89.5 [77.7-101]
F	0.567 (8.9)	0.575 [0.494-0.657]
ka (h-1)	1.25 (13.8)	1.25 [1.02-1.50]
MTT (h)	0.363 (16.4)	0.367 [0.262-0.474]
NN (n)	19.9 (32.2)	21.5 [13.6-31.5]
Inter-individual variability (%)[a, b]		
CL	19.9 (16.6)	20.6 [15.2-25.3]
Vc	76.1 (13.3)	69.8 [51.6-84.7]
Vp	35.7 (12.7)	34.3 [26.5-40.5]
Q	31.0 (39.2)	34.3 [19.2-48.6]
F	23.6 (22.3)	25.0 [16.3-32.2]
MTT	63.2 (24.3)	60.9 [39.9-79.0]
Covariance (F-MTT)[c]	0.0848	0.0952 [0.0356-0.161]
Residual variability (%)		
Proportional error	12.9 (21.3)	13.5 [11.6-14.6]

Parameter estimates are shown with relative standard error of the estimate. CI: confidence-interval, CL: systemic clearance, F: bioavailability, ka: absorption rate constant, MTT: mean transit time, NN: number of transit compartments, OFV: objective function value, Q: intercompartmental clearance, RSE: Relative standard error based on covariance step in NONMEM, SIR: sampling importance resampling, V_c: central volume of distribution, V_p: peripheral volume of distribution

a Calculated as $\sqrt{(e^{\omega^2} - 1)}$

b Eta- shrinkage CL: 12, Vc: 10, Vp: 10, Q: 22, F: 28, MTT: 29

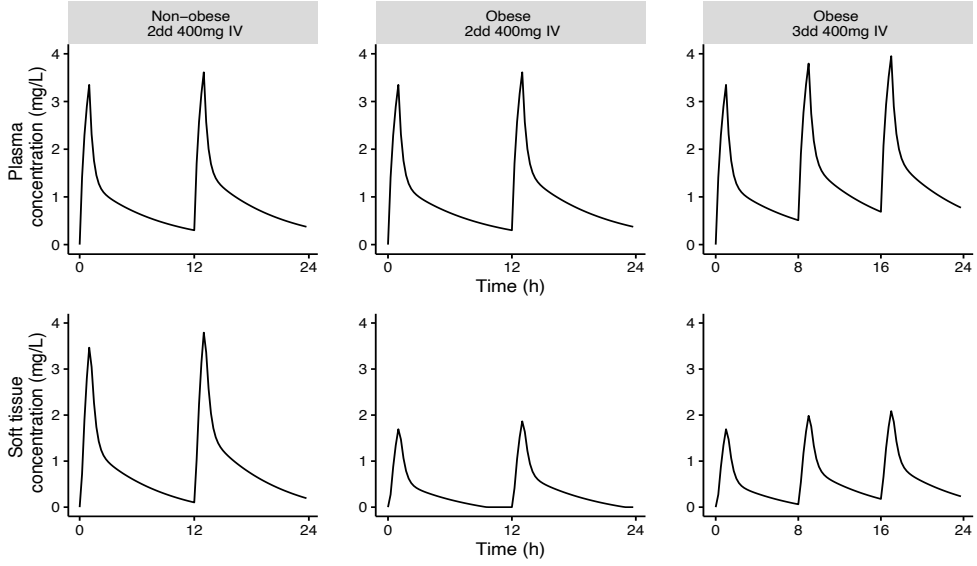
c Correlation coefficient (RSE): 62.9% (19.3%)

The soft tissue concentrations in obese and non-obese patients taken from literature were best described by adding a tissue compartment with first order distribution to tissue and combined zero- and first-order elimination from tissue[8]. To capture the

reduced tissue concentrations in obese individuals versus non obese individuals in this dataset, obesity was successfully implemented as a covariate on the rate constant of transport to tissue (p<0.001, dOFV -174). Results of model building and validation are presented in the Online Resource.

To evaluate the commonly used two or three times daily IV-infusion of 400mg ciprofloxacin dosing regimen, simulated ciprofloxacin concentration-time profiles in plasma for obese and non-obese individuals are shown in Figure 2. The figure illustrates that similar plasma concentrations are obtained after twice daily dosing in obese and non-obese individuals as body weight is not of influence on ciprofloxacin pharmacokinetics in plasma. Using observations by Hollestein *et al.*[8], our model illustrates concentration time profiles that can be expected in soft tissue in obese and non-obese patients upon twice daily or three times daily IV infusion of 400mg ciprofloxacin. After twice daily IV infusion of 400mg the typical AUC_{tissue} on day 3 was 24 mg*h/L for non-obese individuals and 10 mg*h/L for obese individuals.

Figure 2



Concentration-time curves in plasma (top panels) and soft-tissue (lower panels) after a two or three times daily IV infusion of 400mg for a typical non-obese and obese individual.

These results suggest that a higher dosing frequency may be required in obese individuals to achieve an exposure in soft tissue that is similar to that of non-obese individuals. With a standard IV-dose of 400mg, a three time daily dosing regimen yields an AUC_{tissue} of 18mg*h/L and a four times daily regimen an AUC_{tissue} of 26mg*h/L for a

typical obese patient on day 3 of therapy. While both regimens result in exposure in soft tissue that are similar to non-obese patients after twice daily 400mg IV, higher plasma concentrations are observed due to the absence of an influence of weight on clearance in obese compared to non-obese individuals (see figure S6).

Discussion

Collecting prospective data on the pharmacokinetics of antibiotics like ciprofloxacin in (morbidly) obese individuals is highly relevant given the ever-increasing obesity prevalence and the fact that suboptimal concentrations may lead to therapeutic failure and increased antibiotic resistance [1, 20, 21]. This study showed that weight has no significant influence on oral absorption, bioavailability, clearance and volume of distribution of ciprofloxacin in a cohort of individuals with total body weights over a large weight range (57-212kg). No upfront dose adjustment would be warranted for either oral or intravenous administration of ciprofloxacin in (morbidly) obese patients when assuming plasma concentration drives the effect of ciprofloxacin. While there is no information on ciprofloxacin penetration in lung, prostate, urinary tract or gastro-intestinal (GI)-tract of obese patients, the use of literature data in skin and soft tissue shows higher dosages are needed for obese patients to achieve sufficient exposure in soft tissue.

To our knowledge this is the first study to evaluate ciprofloxacin pharmacokinetics in obese patients after oral administration. The bioavailability of 57% (95%CI 49% – 66%) we report is comparable to the 56-77% that is reported in literature[4]. Bioavailability and oral absorption appeared to be unaffected by obesity. The absence of an influence of weight on bioavailability is in agreement with the observation that OATP1 function is unaffected in obese overfed rats[22]. Our findings are in line with previous studies on orally administered drugs in obese patients[6].

Although ciprofloxacin pharmacokinetics in obese patients was studied before, previous studies had shortcomings in their design and showed conflicting results[8,9]. Hollenstein et al. recruited a cohort of obese participants with mean ± SD TBW 122 ± 22.6 kg and mean ± SD BMI 41 ± 7.8 kg/m^2, but used a relatively short sampling time of 6h after infusion, which limits accurate estimation of clearance, the PK parameter that determines drug exposure. In this study, no difference in volume of distribution or clearance between obese and non-obese individuals was reported[8]. Allard *et al.* observed ciprofloxacin pharmacokinetics, for 24 hours after infusion, in less severely obese participants with mean ± SD TBW 111 ± 22.6kg. Nevertheless, a 22% increase in volume of distribution, 21% increase in total ciprofloxacin clearance, and 29% increase in renal ciprofloxacin

clearance was reported in obese participants[9]. We found a non-significant trend of TBW with volume of distribution and no trend of TBW with clearance. We recruited participants with a large weight range (57-212kg), applied a sampling schedule that extends up to 12h in order to estimate clearance, and found no influence of TBW on clearance or volume of distribution despite using state of the art modelling techniques.

For efficacy of antibiotic therapy in general, exposure at the site of infection is paramount. Reduced tissue penetration is mainly driven by ectopic fat disposition and impaired peripheral blood flow. Organs prone to ectopic fat disposition are the subcutis and, at later stages of obesity, the liver, heart, kidneys and pancreas[8, 20]. Ciprofloxacin is used for empirical treatment of prostate, urinary tract, lung and GI-tract infections. Unfortunately, except for the data on soft tissue penetration of ciprofloxacin in obese patients that we considered in our model, there are no data on tissue penetration of ciprofloxacin in obese patients. Reports in non-obese individuals showed that penetration of ciprofloxacin in prostate, GI-mucosa, kidney and epithelial lining fluid was adequate, but showed high inter-individual variability in tissue/plasma ratio [23-27]. While a potential influence of body weight on penetration in target organs cannot be precluded, upfront dose adjustment does not seem warranted for empirical treatment with ciprofloxacin in obese individuals as the prostate, urinary tract, lung and GI-tract are not prone to ectopic fat disposition.

For targeted therapy of skin and soft-tissue infections, sufficient exposure is needed in tissue. Ciprofloxacin penetration in soft tissue measured in skeletal muscle and adipose tissue was impaired in obese individuals compared to non-obese individuals, although the difference in adipose tissue did not reach statistical significance[8]. Cefazolin demonstrated similar behavior as clearance from plasma was unaltered by obesity, while tissue penetration was impaired in obese individuals[28]. Individual concentration time and demographic data of Hollenstein *et al.* were unavailable and only information from the publication could be used[8]. As such, obesity was modeled as a dichotomous covariate preventing inclusion of different levels of obesity into the tissue penetration model. We have assumed that if the simulated ciprofloxacin exposure in plasma for obese and non-obese individuals is similar to observations by Hollenstein *et al.* exposure in soft tissue would also be similar. This approach does allow for quantification of ciprofloxacin exposure in soft tissue but does not allow further exploration of underlying biological principles causing the differences in tissue penetration. Based on the available data, potential inter individual differences in tissue penetration ratio and influence from micro dialysis techniques could not be studied. With inclusion of these limited literature data we show that adequate exposure to ciprofloxacin in soft tissue for obese patients is expected to be achieved after a three times daily regimen for obese individuals with TBW 120 – 160kg and four times daily regimen for individuals with TBW above 160kg.

Nevertheless, the literature data on soft tissue penetration in obese patients were obtained in a single dose study and therefore the predictive performance of our model towards steady-state concentrations in tissue is unknown.

The obese individuals in our study underwent bariatric surgery during the study procedures which in theory might influence the estimation of pharmacokinetic parameters. To minimize the influence of surgery on ciprofloxacin pharmacokinetics, the medication was administered 3 hours before initiation of surgery in order to allow for oral absorption and distribution to be (virtually) complete. In our hospital, bariatric surgery is performed laparoscopically, with a short procedure (usually 30–45 min) involving minimal blood loss (usually < 50 mL). Also, hemodynamic parameters were tightly monitored and regulated during surgery and no major hemodynamic instability was recorded for any of the included individuals in our study. For this reason, we expect that the influence of surgery on the pharmacokinetics is negligible.

Participants in this study were in good health besides being (morbidly) obese and had good renal function. Ciprofloxacin pharmacokinetics in critically ill obese patients and in obese patients with renal dysfunction are therefore outside the scope of this study. In critically ill patients ciprofloxacin clearance showed correlation with MDRD and CG[29,30]. Which estimator of renal function shows best correlation with ciprofloxacin clearance in critically ill obese patients, especially individuals with renal impairment, requires further study.

Conclusion

Based on plasma pharmacokinetics we found no evidence of an influence of obesity on ciprofloxacin pharmacokinetic parameters. Therefore ciprofloxacin dosages do not need to be increased routinely in obese individuals. In case of treatment of infections in tissue where impaired ciprofloxacin penetration is anticipated, higher dosages may be required.

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Supplementary material

Plasma PK-data

Plasma samples were obtained in non-obese patients who received a 500mg oral dose of ciprofloxacin followed by a 400mg 1-hour IV infusion given three hours after the oral administration. Obese patients received a single ciprofloxacin oral or IV dose of 500mg or 400mg over 1-hour, respectively.

Sampling was done according to the scheme in table 1. For non-obese and obese PO individuals, t=0 is the moment of oral administration. For obese IV individuals, t=0 is end of the 1-hour IV infusion.

Table S1: Sampling scheme

Time (min (hours))	Non-obese	Obese IV	Obese PO
5		X	
15		X	
30	X	X	X
60 (1h)	X	X	X
75			X
90	X	X	X
105	X		X
120 (2h)	X	X	X
135	X		X
150	X	X	X
165	X		X
180 (3h)	Start of IV infusion	X	X
210			X
240 (4h)	End of IV infusion	X	X
245	X		
270	X		
300 (5h)	X		X
330	X		
360 (6h)	X	X	
420 (7h)	X		X
480 (8h)	X		
600 (10h)	X		
720 (12h)		X	X
960 (16h)	X		
N samples	17	11	15

Model development

All ciprofloxacin concentration time profiles were modelled using (NONMEM; v7.4.0 with PsN; v4.7.1 and Pirana v2.9.7, R v4.0.3, Rstudio v1.1.383, Xpose v0.4.12, VPC package v1.2.2)[1-3]. Model building consisted of building a structural model, statistical model and covariate model. The structural and statistical models were built simultaneously.

Nested models were discriminated by using the objective value function (OFV). A decrease in OFV >3.84 ($p<0.05$) was considered statistically significant for one degree of freedom. Goodness-of-fit plots (Observed versus population predicted concentrations, Observed versus individual predicted concentrations, conditional weighted residuals (CWRES) versus predicted concentration, CWRES versus time after dose, CWRES versus time), plausibility of parameter estimates, relative standard error of the estimates.

Structural and statistical model

For the oral absorption phase, a LAG-time, Erlang-type absorption, and transit compartment model was evaluated (ADVAN4, ADVAN6) in combination with a one- or two-compartment structural model. Inter-individual variability on individual parameter estimates was assumed to be log-normally distributed and modelled using equation 1 in which the individual parameter estimate for the i^{th} individual is calculated using the population mean θ_{mean} and the random variable η_i (eta) for the i^{th} individual from a normal distribution with a mean of 0 and estimated variance of ω^2.

$$\theta_i = \theta_{mean} \times \exp(\eta_i) \quad (1)$$

Correlation between eta's was evaluated by creating eta-eta scatterplots. If a trend was observed that was not resolved by introduction of covariates on the concerning parameters, correlation was added using an OMEGA BLOCK in the model.

For the residual variability, which could result from model misspecification, essay errors, sampling errors and unexplained sources of variability, three different error model structures were explored using equation 2.

$$Y_{ij} = C_{pred,ij} + (C_{pred,ij} \times \varepsilon 1_{ij}) + \varepsilon 2_{ij} \quad (2)$$

Y_{ij} is the observed concentration and $C_{pred,ij}$ is the predicted concentration for the j^{th} observation of the i^{th} individual. The combined error model consists of a proportional error ($\varepsilon 1_{ij}$) and an additive error ($\varepsilon 2_{ij}$). Both $\varepsilon 1_{ij}$ and $\varepsilon 2_{ij}$ are values from a normal distribution with a mean of zero and estimated variance of σ^2. Additive and proportional error models were tested by fixing ε1 or ε2 to 0, respectively.

Covariate analysis

Weight on V_d and CL and GFR on CL were selected as covariates to be tested in the covariate analysis based on physiological plausibility. Additionally, possible correlations between pharmacokinetic parameters and covariates (sex, age, race, total body weight, lean body weight, GFR, MDRD, $MDRD_{di}$, CKD, CKD_{di}, CG_{TBW}, CG_{LBW}, history and duration of obesity) were assessed by plotting individual eta-values versus individual values of the covariate if shrinkage was <20%. If a trend was observed, the covariate effect was formally tested in the covariate analysis.

Continuous covariates were tested using equation 3 where P_i and P_p represent the individual and population parameter estimates, respectively. COV_i represents the individual value of the covariate to be tested and $COV_{standard}$ represents a population

standard for the concerning covariate, which represents the median value of GFR in the dataset or 70kg for TBW. X represents an exponent that is being estimated.

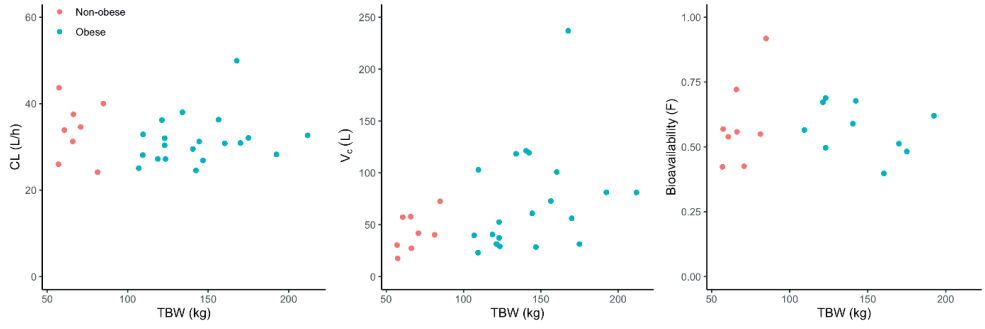
$$P_i = P_p \times (COV_i / COV_{standard})^X \qquad (3)$$

Covariates were entered into the model and statistical testing was performed using forward inclusion ($p<0.05$; OFV decrease >3.84 for one degree of freedom) and backward elimination ($p<0.001$; OFV increase>10.8 for one degree of freedom). Reduction of inter-individual variability, evaluation of diagnostic plots and eta-plots were used to determine if the covariate should be incorporated in the model.

Model validation

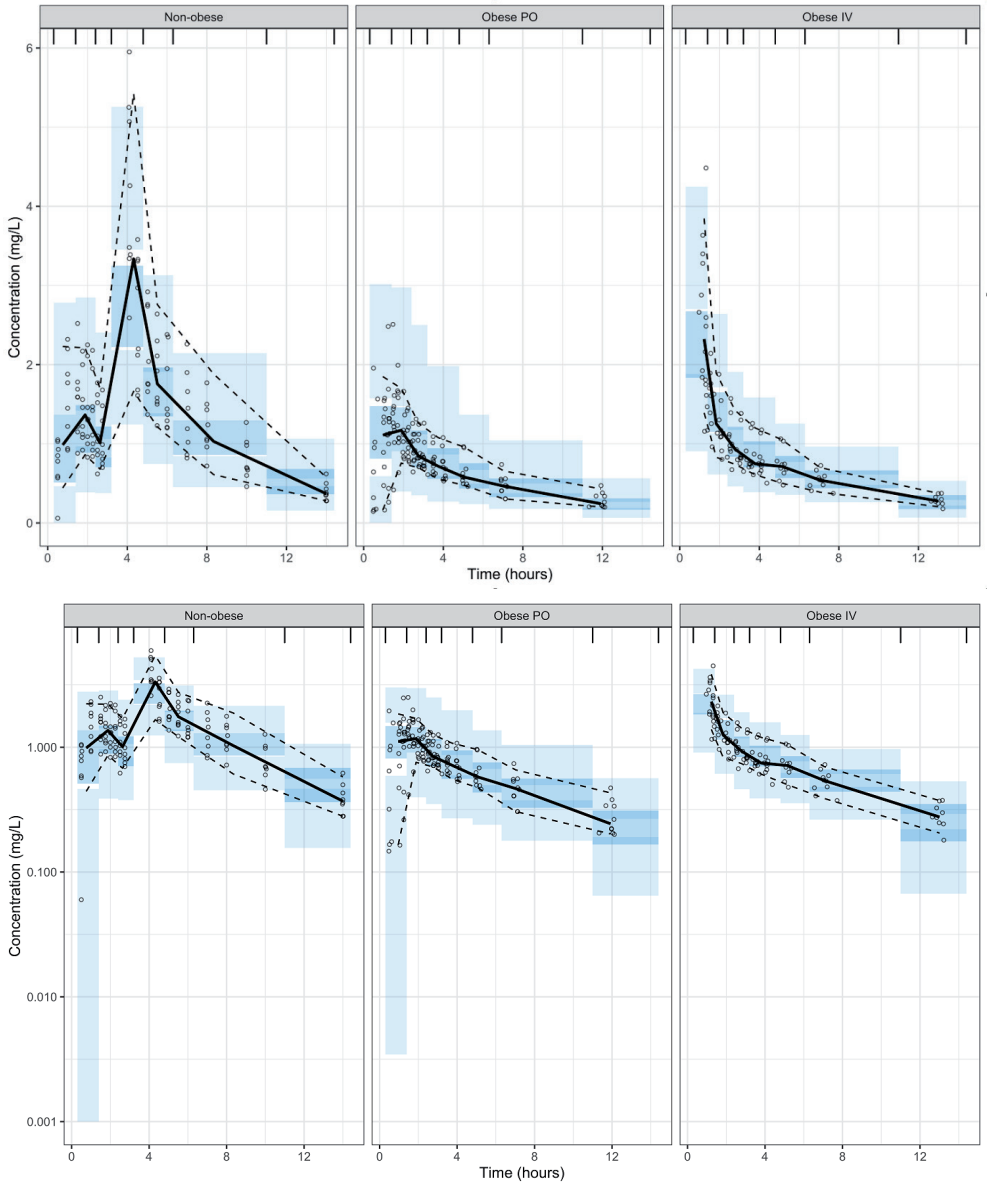
Figure 1 shows the Empirical Bayes Estimates on clearance and volume of distribution versus total body weight. Clearance shows no trend with bodyweight. Central volume of distribution does show a small trend with TBW, but inclusion of TBW as a covariate on V_c did not reach statistical significance.

Figure S1



Empirical Bayes Estimates for clearance (CL), central volume of distribution (V_c) versus total body weight. Obese patients (n=20) are shown in teal, non-obese (n=8) are shown in red.
The visual predictive check stratified for non-obese versus obese and route of administration for the obese subgroup shows internal validity of the model (figure 2) as observations and predictions are in agreement.

Figure S2



Visual predictive check of the final model stratified by subgroup (non-obese n=8, obese PO n=10, obese IV n=10) on linear scale at the top and on logarithmic scale at the bottom. The observed data are shown as circles with the median and 2.5th and 97.5th percentile of the observed data shown as a solid black line and the upper and lower dashed lines, respectively. The blue areas represent the 95% confidence interval of the simulated median (dark blue) and 5th and 95th percentile (light blue) of the simulated concentrations based on 1000 simulations of the original dataset. Vertical lines at the top of the panels represent the bins.

Model extension

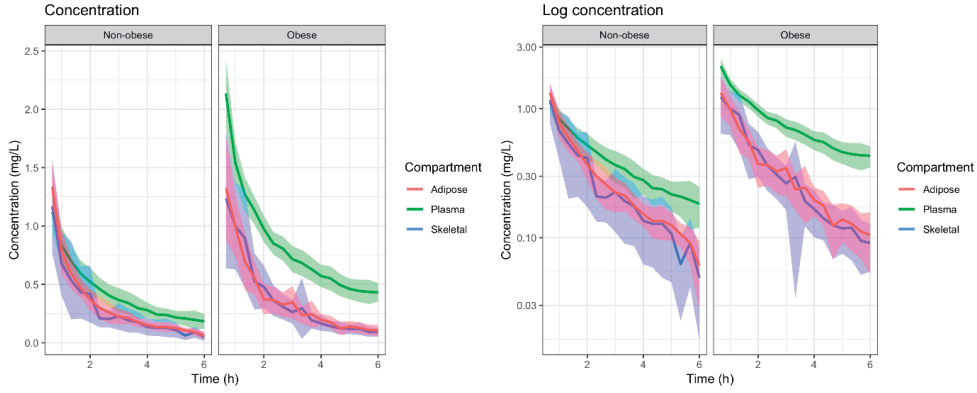
To account for reduced ciprofloxacin tissue penetration in obese patients as was reported by Hollenstein *et al.*, the ciprofloxacin model was extended with tissue concentrations from literature to explore dosing regimens leading to similar ciprofloxacin exposure in skin and soft tissue for non-obese and obese individuals[4].

Methods

Data

Raw data of individual plasma and tissue concentration-time curves published by Hollenstein *et al.* were unavailable. Therefore, the plots reported by Hollenstein *et al.* were digitized and concentration-time curves for plasma, adipose tissue, and skeletal muscle were obtained for the obese and non-obese subgroup. Mean concentration time-profiles in skeletal muscle and adipose tissue overlapped (figure 3). Therefore, the data from adipose and skeletal muscle were pooled to estimate mean tissue concentration for a mean obese and non-obese individual. Hollenstein *et al.* sampled from tissue over 20 minute intervals using microdialysis. Given the dense sampling procedure, the observed tissue concentrations were assumed to be made at the midpoint of the respective 20 minute interval.

Figure S3



Digitized mean ciprofloxacin concentration-time profiles in plasma, adipose tissue and skeletal muscle of non-obese and obese individuals as obtained from Hollestein et al.[4] Data are presented on linear (left panels) and log (right panels) scale with ciprofloxacin mean concentration + 95% CI for the mean.

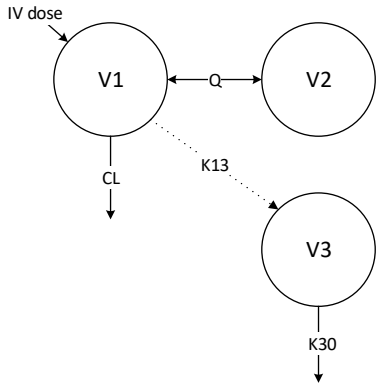
Model building

The model was extended with an additional compartment for tissue concentrations using ADVAN9. Structural effects from our own model were fixed at the values presented

in the final model and inter individual variability was fixed at 0 because mean data were analyzed.

To describe the tissue concentrations, the structural model (figure 4) was used to estimate parameters for k13 and k30. The volume of the tissue compartment (V3) was set equal to the volume of the central compartment (V1).

Figure S4 Structural model



Schematic representation of the model structure used to estimate tissue concentrations. K13 is shown as a dashed line as k13 is excluded from the differential equation describing the change in concentration in the central compartment.
V1: central volume of distribution, V2: peripheral volume of distribution, V3: tissue volume of distribution, CL: Clearance from central compartment, Q: Intercompartmental clearance, K13: rate constant for transport from central to tissue compartment, K30: rate constant for elimination from tissue.

Transport from the central (V1) to the tissue compartment (V3) was excluded in the differential equation for the central compartment, thereby implicitly assuming the amount of drug going to the peripheral compartment to be negligibly small compared to the amount of drug present in the central compartment. Different clearance functions were tested to describe the mean tissue concentration in obese and non-obese patients (table 2). Michaelis-Menten elimination was tested using equation 4.

$$k_{30} = \frac{V_{max} * C}{K_m + C} \qquad (4)$$

Table S2: Combinations of rate constants tested to describe tissue concentrations

Transport from plasma to tissue (k_{13})	Elimination from tissue (k30)
First-order	First-order
First-order	Michaelis-Menten
Michaelis-Menten	First-order
First-order	Combined first- and zero-order

Obesity was tested as a covariate on all rate constants using forward inclusion followed by backward deletion. For Michaelis-Menten kinetics both a separate Vmax and a different km were tested for obese and non-obese patients.

For forward inclusion $p<0.05$ (OFV decrease >3.84 for one degree of freedom) and for backward elimination $p<0.001$ (OFV increase >10.8 for one degree of freedom) were considered statistically significant.

For visual predictive checks, calculated tissue and plasma concentrations in obese and non-obese patient after the dosing regimen applied by Hollenstein et al. (2.85 mg/kg TBW ciprofloxacin infused over 1 hour) were plotted versus Hollenstein observations (mean ± s.e.).

In order to compare exposure, the Area Under the Concentration-time curve (AUC) was calculated using the $DES block in NONMEM.

Model based dosing

The extended model was used to evaluate dosing regimens for obese patients that lead to steady state exposure in tissue similar to non-obese patients. For the obese patients an estimated $AUC_{48\text{-}72h}$ at 75-125% of AUC in non-obese patients was considered acceptable. Weight based doses rounded to the nearest multiple of 400mg were evaluated for practical convenience.

Results

Model building

The data observed by Hollenstein *et al.* were best described by extending the model with a tissue compartment with first order transport to and a combined first- and zero-order elimination from tissue for both obese and non-obese individuals[4]. Obesity was identified as a covariate on the rate constant of transport from the central compartment to the tissue compartment (k_{13}). Structural parameters are presented in table 3.

A visual predictive check from the extended model is presented in figure S5. Both the high concentrations, low concentrations and trend in tissue concentration is well described over 6 hours after administration for both the obese and non-obese subgroup.

Table S3: Parameters of the model describing tissue concentrations

Parameter	Value (% RSE)
CL (L/h)	31.7 FIX
V_1 (L)	55.4 FIX
V_2 (L)	144 FIX
Q (L/h)	87.8 FIX
k_{13} non-obese (h^{-1})	8.18 (14.8)
k_{13} obese (h^{-1})	4.3 (15.6)
k_{30} first order (h^{-1})	6.71 (16.8)
k_{30} zero order (h^{-1})	101 (14.3)
Proportional error (%)	15.1 (10.8)

CL: Clearance, V1: central volume of distribution, V2: peripheral volume of distribution, Q: intercompartmental clearance between V1 and V2, k13: rate constant of clearance from central to tissue compartment, k30: rate constant of elimination from tissue

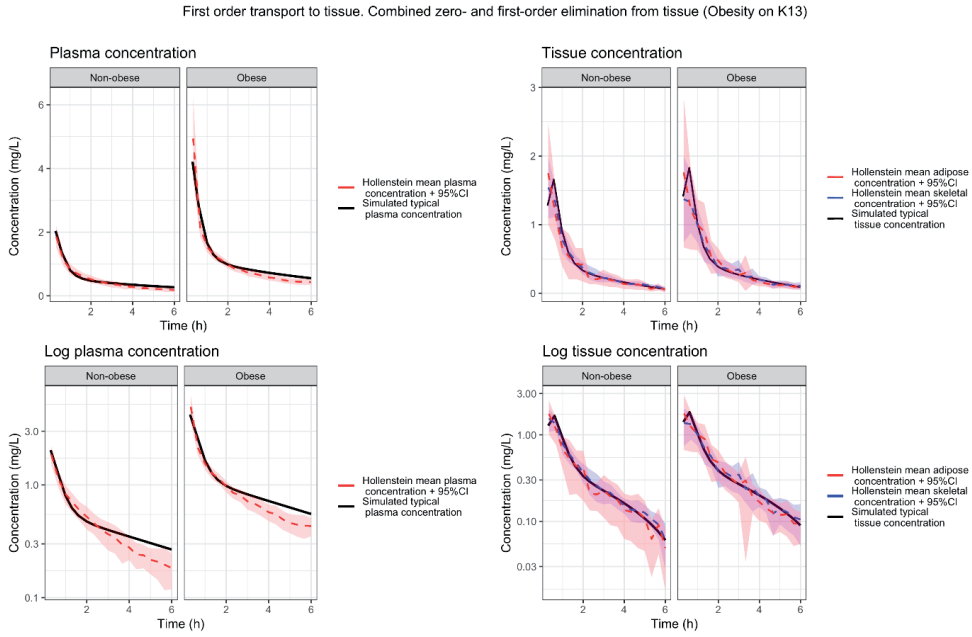
Tissue penetration ratio

The model-based tissue penetration ratio from the final extended model 0-6 hours after infusion of 2.85mg/kg as dosed by Hollenstein et al. was 0.41 for a typical obese individual and 0.74 for a typical non-obese individual[4]. This is similar to the results presented by Hollenstein et al[4]. where the mean tissue penetration ratio for the obese subgroup was 0.45 for skeletal muscle (9% deviation) and 0.46 for adipose tissue (11% deviation). For the non-obese subgroup tissue penetration ratio was 0.82 for skeletal muscle (10% deviation) and 0.86 for adipose tissue (14% deviation)).

Model based dosing

For obese patients, a dosing regimen of three or four times daily IV infusion of 400mg is expected to result on the third day of treatment in exposure in tissue similar to twice daily IV infusion of 400mg in non-obese patients. Typical exposure for the proposed dosing regimen is presented in table 4.

Figure S5



The upper panels display plasma- and tissue concentrations split for non-obese and obese patients. The lower panels display log plasma- and tissue concentration split for non-obese and obese patients. Observations and simulations are based on a 2.85mg/kg IV infusion in 1 hour.
The left panels represent observed (dashed line with shaded area) and simulated plasma concentration (black line).
The right panels represent tissue concentrations. The simulated typical concentrations are represented by the black line. The data observed by Hollenstein are presented as mean (dashed red and blue lines) and 95%CI for the mean (shaded red and blue areas).

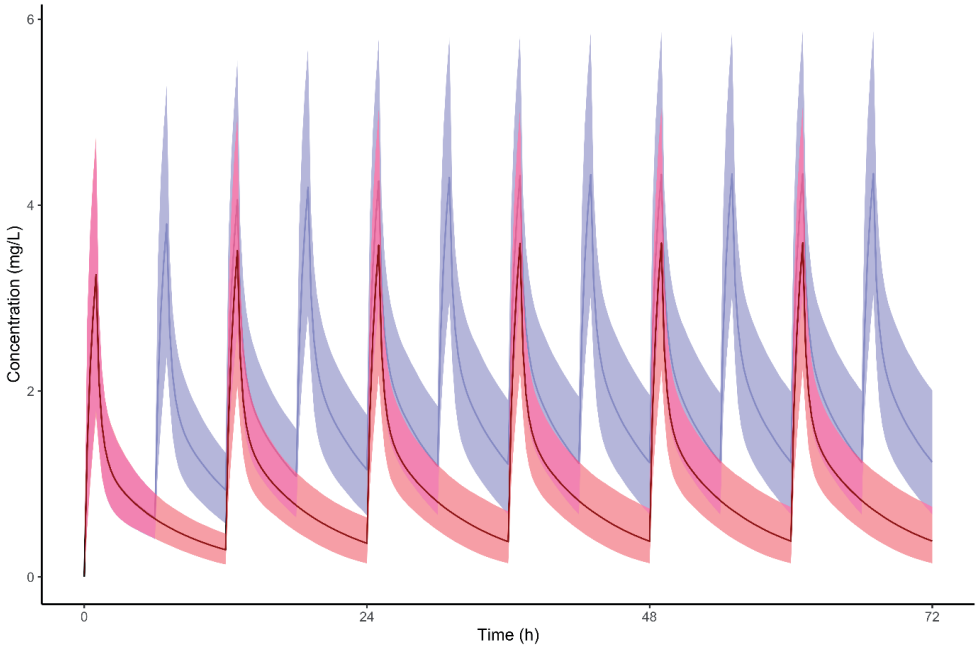
The proposed dosing regimen results in increased exposure in plasma in obese patients. The upper limit of safety for ciprofloxacin plasma concentration is not well defined but a safety threshold of AUC<100 mg*h /L was used before[5]. The typical exposure in plasma using the 4 times daily 400mg IV infusion is 50 mg*h/L which is well within that safety limit. Increased plasma C_{max} has also been proposed as a marker for increased side effects[4]. Figure 6 shows ciprofloxacin C_{max} is increased from 3.6 (upper limit 95% prediction interval 5.0mg/L) to 4.3 (upper limit 95% prediction interval 5.9mg/L). The mild increase in plasma C_{max} is not considered clinically relevant.

Table S4: Exposure in plasma and tissue on day 3

	Non-obese	Obese 120-160kg	Obese >160kg
Dosing regimen	2dd 400mg	3dd 400mg	4dd 400mg
Plasma $AUC_{day\ 3}$ (mg*h/L)	25	38	50
Tissue $AUC_{day\ 3}$ (mg*h/L)	24	18	26

Exposure in plasma and tissue on day 3 after weight based dosing for typical non-obese, obese patient 120-160kg, and obese patient >160kg. Dosing regimen consists of 2-4 times daily infusion of 400mg. AUC: Area under the concentration-time curve on the third day of therapy (48-72h).

Figure S6



Ciprofloxacin plasma concentration versus time profiles for twice daily 400mg IV which is currently used as standard dose in obese and non-obese (red) and 400mg four times daily in individuals with TBW >160kg (blue). Plasma concentrations are shown as median (line) and 95% prediction interval(PI) (shaded area). The median peak concentration at steady state for the twice daily regimen is 3.6mg/L (upper limit 95% PI 5.0mg/L) and 4.3mg/L (upper limit 95% PI 5.9mg/L) for the four time daily regimen. Data are based on a stochastic simulation with n=5000 per dosing regimen

NONMEM control stream for the final model
Plasma concentration model

```
;; 1. Based on: run01
;; 2. Description: Ciprofloxacin oral absorption and plasma concentration model
;; x1. Author: KvR
;; 3. Label:

$PROBLEM PK
$INPUT ID TIME AMT RATE DV CMT MDV TAD

$DATA data.prn IGNORE=@
$SUBROUTINES ADVAN6 TOL9
$MODEL
COMP=(ABS)
COMP=(CENT)
COMP=(PERI)

$PK
IF(AMT.GT.0.AND.CMT.EQ.1)PODO=AMT    ; ORAL DOSING
IF(AMT.GT.0.AND.CMT.EQ.2)PODO=0      ; IV DOSING

; DISPOSITION MODEL
CL = THETA(1) * EXP(ETA(1))          ; CLEARANCE
V2 = THETA(2) * EXP(ETA(2))          ; CENTRAL VOLUME OF DISTRIBUTION
Q = THETA(3) * EXP(ETA(3))           ; INTERCOMPARTIMENTAL CLEARANCE
V3 = THETA(4) * EXP(ETA(4))          ; PERIPHERAL VOLUME OF DISTRIBUTION

; BIOAVAILABILITY MODEL
F1 = 0                               ; THE AMOUNT IS USED IN THE ABSORPTION PROCESS
F2 = 1
BIO = THETA(5) * EXP(ETA(5))         ; BIOAVIAILABILITY

; ABSORPTION MODEL
KA = THETA(6)                        ; ABSORPTION RATE CONSTANT
MTT = THETA(7) * EXP(ETA(6))         ; MEAN TRANSIT TIME
NN = THETA(8)                        ; NUMBER OF TRANSIT COMPARTMENTS
KTR = (NN+1)/MTT                     ; TRANSIT RATE CONSTANT
K23 = Q/V2
K32 = Q/V3
```

```
K20 = CL/V2                    ; ELIMINATION RATE CONSTANT
NFAC =SQRT(2*3.1415)*NN**(NN+0.5)*EXP(-NN) ; STERLING APPROXIMATION
S2 = V2
S3 = V3

$DES
DADT(1)=BIO*PODO*KTR*(KTR*T)**NN*EXP(-KTR*T)/NFAC-KA*A(1)
DADT(2)=KA*A(1)-K20*A(2)-K23*A(2)+K32*A(3)
DADT(3)=K23*A(2)-K32*A(3)

$ERROR
IPRED= A(2)/S2                 ; INDIVIDUAL PREDICTION
Y = IPRED + IPRED*EPS(1) + EPS(2)
IRES=DV-IPRED

$THETA
(0, 31.7) ; CL
(0, 55.4) ; V2
(0, 87.8) ; Q
(0, 144) ; V3
(0, 0.567) ; BIO
(0, 1.25) ; KA
(0, 0.363) ; MTT
(0, 19.9) ; NN

$OMEGA
 0.0389         ; IIV CL
 0.457          ; IIV V2
 0.0916         ; IIV Q
 0.120          ; IIV V3
$OMEGA BLOCK(2)
 0.0542         ; IIV BIO
 0.0848 0.335   ; IIV MTT
$SIGMA
 0.0165         ; Proportional error PK
 0 FIX          ; Additional error PK
$EST METHOD=1 INTER MAXEVAL=999 NOABORT SIGL=9 NSIG=3 PRINT=5 POSTHOC
$COV PRINT=E
$TABLE ID TIME DV MDV EVID IPRED ETAS (1:LAST) CWRES CL V2 TAD ONEHEADER
NOPRINT FILE=sdtab01
```

NONMEM Control Stream for the Final Model
Plasma and tissue concentration model

```
;; 1. Based on: run02
;; 2. Description: First order transport to tissue. Combined zero- and first-order elimination
from tissue (Obesity on K13)
;; x1. Author: KvR
;; 3. Label:
$PROBLEM PK
$INPUT ID TIME AMT RATE DV CMT MDV GRP ; GRP==0; obese, GRP==1; non-obese
$DATA data.prn IGNORE=@
$SUBROUTINES ADVAN9 TOL9
$MODEL
COMP=(CENT)
COMP=(PERI)
COMP=(TISSUE)

$PK
;BASE MODEL
CL      = THETA(1) * EXP(ETA(1))  ; CLEARANCE
V1      = THETA(2) * EXP(ETA(2))  ; CENTRAL VOLUME OF DISTRIBUTION
Q       = THETA(3) * EXP(ETA(3))  ; INTERCOMPARTMENTAL CLEARANCE
V2      = THETA(4) * EXP(ETA(4))  ; PERIPHERAL VOLUME OF DISTRIBUTION
K10 = CL/V1                       ; ELIMINATION RATE CONSTANT
K12 = Q/V1
K21 = Q/V2

;HOLLENSTEIN EXTENSION
V3      = V1
TVK13   = THETA(5)                ; FIRST ORDER TRANSPORT TO TISSUE NON-OBESE
IF(GRP.EQ.0)TVK13 = THETA(6)      ; FIRST ORDER TRANSPORT TO TISSUE OBESE
K13     = TVK13
K301    = THETA(7)                ; FIRST ORDER ELIMINATION FROM TISSUE
K300 = THETA(8)                   ; ZERO ORDER ELIMINATION FROM TISSUE
S1 = V1
S2 = V2

$DES
DADT(1)=-K12*A(1)+K21*A(2)-K10*A(1)
DADT(2)=K12*A(1)-K21*A(2)
```

```
DADT(3)=K13*A(1)-K301*A(3)-K300

$ERROR
IPRED=F
IF (CMT.EQ.1) Y=IPRED+IPRED*ERR(1)
IF (CMT.EQ.3) Y=IPRED+IPRED*ERR(2)
IRES=DV-IPRED

$THETA
(31.7) FIX              ; CL
(55.4) FIX              ; V1 CENT
(87.8) FIX              ; Q
(144) FIX               ; V3 PERI
(8.18)                  ; K13 NON-OBESE
(4.30)                  ; k13 OBESE
(6.71)                  ; K30 FIRST ORDER
(101)                   ; K30 ZERO ORDER

$OMEGA
0 FIX
0 FIX
0 FIX
0 FIX

$SIGMA
 0.0165 ; PROPORTIONAL ERROR PK PLASMA
 0.0224 ; PROPORTIONAL ERROR PK TISSUE

$EST METHOD=1 INTER MAXEVAL=999 SIGL=9 NSIG=3 PRINT=5 POSTHOC
$COV PRINT=E

$TABLE ID TIME DV MDV EVID IPRED ETAS (1:LAST) CWRES CL V2 TAD ONEHEADER
NOPRINT FILE=sdtab02
```

References

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2 Keizer R J RJ. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT: Pharmacometrics and Systems Pharmacology 2013-6-26;2.
3 R Core Team. R: A language and environment for statistical computing. 2015.
4 Hollenstein UM, Brunner M, Schmid R, Müller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord 2001;25(3):354-358.
5 Gieling EM, Wallenburg E, Frenzel T, de Lange DW, Schouten JA, ten Oever J, et al. Higher Dosage of Ciprofloxacin Necessary in Critically Ill Patients: A New Dosing Algorithm Based on Renal Function and Pathogen Susceptibility. Clin Pharmacol Ther 2020;108:770-774.

CHAPTER 4

4

Patients with obesity should be recognized as a special patient population during drug development of antibacterial and antifungal agents; a call to action

Koen P. van Rhee, Catherijne A.J. Knibbe, Paul D. van der Linden, Roger J.M. Brüggemann



Abstract

Individuals with obesity are at increased risk of developing infectious diseases. Timely administration of an effective dose of an antimicrobial agent is paramount to safeguard optimal therapy. For this purpose, special patients populations at risk for altered exposure such as renal- or hepatic impairment are studied during drug development. Strikingly, there is no such evaluation in individuals with obesity despite a potential influence on exposure and a global obesity prevalence of 13%.

Optimal clinical decision making in patients with obesity is impossible without prior study of the drug of interest in this population. This statement is strengthened by an evaluation of 19 antimicrobial agents that showed tremendous variability in the influence of weight on clearance.

In contrast to patient with renal- or hepatic impairment who are mainly at risk of overexposure, individuals with obesity can be at risk of both under- and overexposure. Gaining knowledge on the influence of body weight on clearance during early phases of drug development may allow for optimization of other phases of research, potentially increasing success rate of the drug, and provides clinicians with vital information as soon as it reaches the market.

Antimicrobial therapy should be tailored to obesity related (patho)physiological changes and to reach this goal, obese individuals should be studied during drug development.

Introduction

Clinical problem

Patients with obesity (Body Mass Index (BMI) >30kg/m^2) are at increased risk of nosocomial infections such as surgical site infections, pneumonia and Clostridium Difficile colitis and are also more likely to develop severe complications from infections[1]. Moreover, patients with obesity show increased length of stay in the intensive care unit although mortality is not necessarily increased[1]. There is a great need to provide optimal care to patients with obesity with infectious diseases although clear guidance on how therapy should be individualized is often lacking. We are of the opinion that antimicrobial therapy should be tailored according to obesity associated physiological changes that impact drug pharmacokinetics thereby assuring sufficient exposure and thus maximize efficacy and simultaneously minimizing toxicity.

Obesity

Global obesity prevalence among adults was estimated at 650 million in 2016, 13% of the world population, and tripled since 1975[2, 3]. Historically, prevalence was concentrated in high-income countries but is on the rise in low- and middle-income countries, especially in urban areas[3]. Although obesity is defined as a BMI >30kg/m^2, the population of individuals with obesity is heterogeneous and could be viewed on a continuous scale as different classes of obesity are distinguished ranging from BMI 30-35kg/m2 for class I to BMI >40kg/m^2 for class III[2]. An overabundance of adipose tissue is the key characteristic of obesity although physiological changes may simultaneously happen in various organ systems like the kidneys, liver and the cardiovascular system[3, 4].

Glomerular filtration rate increases at an early stage of obesity while it decreases in the long term. Additionally, tubular secretion is enhanced in individuals with obesity. Cardiac output increases, which leads to increased liver blood flow that is an important determinant for clearance of medium to high extraction ratio drugs. The intestinal and hepatic Cytochrome P450 (CYP) 3A4 and 2C19 mediated metabolic capacity is reduced while CYP 2E1 and phase II-metabolism are enhanced while CYP 1A2 and 2C9 activity remains uninfluenced by obesity[4, 5]. Moreover the expression of drug transporters like Organic Anion Transporter, Organic Anion Transporting Polypeptides and Multidrug Resistance Protein 2 and 3 may be either suppressed or increased by obesity[4].

Acute infection itself may simultaneously influence clearance as CYP 1A2, 2C19 and 3A activity is increased while 2B6 and 2C9 activity is decreased[5]. Fat disposition in individuals with obesity mainly takes place in the subcutis, abdominal visceral depot, heart, liver, pancreas and kidney. For the treatment of infections in these organs, increased systemic exposure in plasma may be needed to overcome impaired tissue penetration

as was demonstrated for several antimicrobial agents using clinical microdialysis studies[3, 6-8]. Nevertheless, it remains unclear if higher plasma concentrations lead to improved clinical– or microbiological cure.

Investigations on the plasma pharmacokinetics are of important relevance given the difficulties measuring exposure at the site of infection. Plasma exposure or Area Under the Curve (AUC) in steady state is determined by the ratio of clearance and the maintenance dose. For patients with obesity both the influence of body weight on clearance and the dosing regimen, i.e. mg/kg body weight or fixed dose, determine whether an adjusted maintenance dosage is required. An increased volume of distribution would prolong the time to steady state conditions and reduces peak concentrations. A common assumption is that lipophilicity can be used to predict changes in volume of distribution for patients with obesity, however particularly for lipophilic drugs changes are unpredictable and there is high inter-drug variability. Obesity associated changes in volume of distribution need to be taken into account for drugs with long half-life or drugs that depend on peak concentration[9]. For dose adjustments in individuals with obesity clearance is the primary parameter of interest as changes directly influence exposure.

Influence of obesity on clearance of antibacterial and antifungal agents

Non-infectious individuals with obesity

To motivate our position presented in this viewpoint, literature on the influence of body weight on clearance of commonly used antibiotic and antifungal agents in otherwise healthy, i.e. non-infectious, individuals with (morbid) obesity was reviewed[6, 7, 10-26]. Studies reporting on intravenous (iv) administered drugs were included and those only providing clearance for an obese and non-obese cohort without specifying an equation describing clearance over a large weight span were excluded. The fold increase in clearance between a 70kg and 140kg individual was calculated based on the equation for clearance reported in the respective studies. In line with typical criteria for bioequivalence a 1.0 – 1.25 fold increase in clearance may be considered a non-significant influence, a 1.25 – 1.5 fold increase a moderate influence and >1.5 fold increase may be considered a strong influence of body weight on clearance. The 140kg reference weight corresponds with the 95th percentile body weight of Americans in 2016[27].

We identified 19 reports describing the influence of body weight on clearance of antimicrobial agents, i. e. 13 antibacterial agents and 6 antifungal agents. Either a non-

significant, moderate or a strong influence of weight on clearance was identified for 7/19 (37%), 8/19 (42%) and 4/19 (21%) antimicrobial agents, respectively[6, 7, 10-26].

The results are visualized in Figure 1, in which clearance for a typical 70 kg individual was set to 1.0. Each line represents the fold increase in clearance with increasing body weight for the respective antimicrobial agent. A large heterogeneity in influence of increasing body weight on clearance is shown. A twofold increase in clearance corresponds with a 50% decrease in exposure (measured as AUC) for patients with a body weight of 140 versus 70 kg receiving an equal dose. The grey area in Figure 1 represents a moderate influence of body weight on clearance, the area below and above represents non-significant and strong influence, respectively. If non-weight based patient characteristics (age, height or serum creatinine) are predictive for clearance, the median value from the study population was fixed in order to visualize the influence of bodyweight on clearance. As a result, clearance may differ for patients with the same weight if difference in age, height or serum creatinine are present as is the case for cefazolin, ceftarolin, daptomycin, meropenem, piperacillin and tobramycin. From the figure it can be deduced that predicting the influence of body weight on clearance is challenging as even within the therapeutic classes of aminoglycosides, cephalosporins, echinocandins and triazoles pronounced differences are observed which cannot be explained by hepatic versus renal clearance or differences in lipophilicity, protein binding or molecular weight.

Optimizing exposure; connecting obesity and dosing strategy

Body weight and dosing strategy

Exposure to antimicrobial agents in steady state across different body weights is determined by both the influence of body weight on clearance (as depicted in figure 1) and the employed dosing strategy, i.e. fixed dosing or mg/kg body weight. In individuals with obesity, it is as such of particular importance that dose adjustments match the direction and magnitude of effect of weight on clearance. In Table 1 we show that applying the labelled dosing strategy (fixed dosing or mg/kg dosing) to individuals with obesity for the antimicrobial drugs from Figure 1 would introduce a risk of underexposure for 7/19 (37%) antimicrobial agents and a risk of overexposure for 4/19 (21%) antimicrobial agents. Four different scenarios are distinguished in data presented in Table 1; fixed dosing regimen &body weight not associated with increased clearance, fixed dosing regimen & body weight associated with increased clearance, weight based dose & body weight not associated with increased clearance and mg/kg dose & body weight associated with increased clearance. These scenarios are discussed below for the selected 19 antimicrobial agents.

Fixed dosing regimen & body weight not associated with increased clearance

The drugs amoxicillin, cefazolin, ciprofloxacin, moxifloxacin, piperacillin and tigecycline, are given in a fixed dose and their clearance is not influenced by bodyweight[6, 7, 11, 20, 22, 26]. Similar exposure in plasma is expected across all body weights.

Fixed dosing regimen & body weight associated with increased clearance

The drugs anidulafungin, caspofungin, ceftarolin, fluconazole, meropenem, micafungin, posaconazole and tedizolid are also given at fixed dosages, yet their clearance is reported to be influenced by body weight and therefore individuals with obesity may be at risk of underexposure[10, 12, 15, 18, 19, 21, 24, 25]. These drugs may require higher maintenance dosages when the same exposure is aimed for, yet the need and magnitude of dose increase depends on the exact influence of body weight on clearance and the width of the therapeutic window.

Weight based dosing regimen & body weight not associated with increased clearance

Amphotericin B is dosed as mg/kg whereas no influence of body weight on clearance was identified in individuals up to 177kg. As a result, individuals with obesity are at risk of overexposure if doses are not capped at a body weight of 100kg[14].

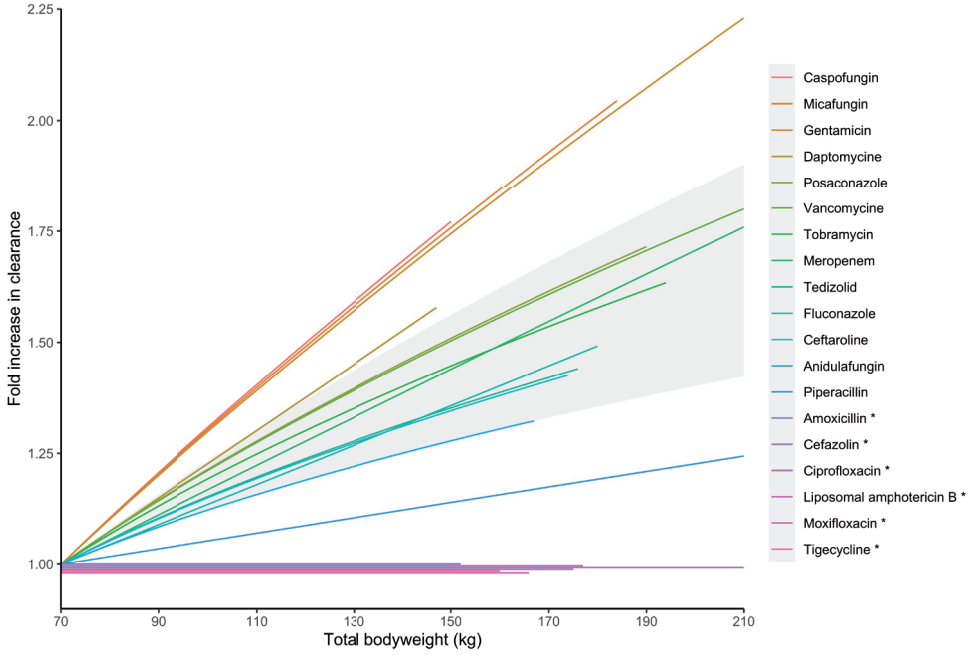
Weight based dosing regimen & body weight associated with increased clearance

For the drugs daptomycin, gentamicin, tobramycin and vancomycin a weight based dosing regimen is employed and weight is of influence on clearance[13, 16, 17, 23]. A mg/kg based dosing regimen provides a linear dose increase with body weight. Nevertheless, clearance may not necessarily increase linearly with bodyweight (Figure 1). As such a mg/kg dose leads to overexposure for individuals with extreme body weights. In order to mitigate the risk of overexposure, alternative body size descriptors like adjusted body weight (ABW) or Lean Body Weight (LBW) may be used to calculate dosing weights as these metrics also increase in a non-linear manner with body weight, similar to the non-linear increase of clearance with bodyweight. The heterogeneity in figure 1 illustrates that no single alternative body size descriptor is suited for use as a universal body size descriptor for predicting clearance in individuals with obesity. Moreover, care is to be taken when using LBW for this purpose, as the inclusion of gender in the calculation of LBW may introduce undesired differences in exposure between men and women[28-30, 32].

For these antimicrobial agents the width of the therapeutic window determines if dose adjustment is needed. Daptomycin has a relatively wide therapeutic window although

doses beyond 500mg are associated with creatinine phosphokinase elevation[31]. Gentamicin on the other hand has a narrow therapeutic window and is usually dosed on ABW in clinical practice. Interestingly this approach introduces a risk of underexposure in individuals with severe obesity and consequently may be dosed on a nomogram that ensures similar exposure across different body weights[17, 32].

Figure 1: Influence of increasing body weight on clearance of antibacterial and antifungal agents expressed as fold increase compared to a typical 70kg individual



*Each line represents an antimicrobial agent visualizing the fold increase in clearance from plasma with increasing body weight. * Amoxicillin, cefazolin, ciprofloxacin, liposomal amphotericin B, moxifloxacin and tigecycline show no influence of body weight on clearance and therefore overlap at Fold increase in clearance = 1.0.*

The grey shaded are represents a moderate influence of body weight on clearance. A fold increase in clearance below the grey area represents no significant influence on clearance, a fold increase in clearance above the grey area represents a strong influence of body weight on clearance.

For cefazolin, ceftarolin, daptomycin, meropenem, piperacillin and tobramycin drivers of clearance were identified that are not strictly weight based (age, height, serum creatinine); for these drugs values of the respective drivers were fixed at the median value in order to visualize the influence of body weight on clearance. The length of the line corresponds with the maximum total body weight in the study population, with a maximum of 210kg.

(Critically) ill patients with obesity

Real-world data from (critically) ill patients with obesity treated with amoxicillin, cefazolin, daptomycin, fluconazole, gentamicin, meropenem, micafungin, moxifloxacin,

piperacillin and vancomycin show that, besides body weight, patient characteristics like renal function, renal replacement therapy, admission to ward or ICU, age and class of obesity may be associated with altered clearance[31-44].

The influence of body weight on clearance in (critically) ill patients with obesity was similar to the influence identified for their non-infectious counterparts for most antimicrobial agents. Nevertheless, for meropenem several studies in critically ill patients did not report an influence of weight on clearance hence dose modification solely based on body weight does not seem warranted[36, 37]. Fixed dosing of daptomycin in (critically) ill patients with obesity is associated with a lower incidence of creatinine phosphokinase elevation, despite a significant influence of weight on clearance[31]. For cefazolin it remains unclear if increased doses for surgical prophylaxis lead to improved outcome in individuals with obesity for procedures >4 hours despite impaired tissue penetration[34].

A major strength of studies in non-critically ill patients with obesity is the wide weight range compared with studies in (critically) ill patients. This allows for precise characterization of the influence of body weight on clearance while minimizing the influence of other potentially relevant influences on clearance like varying renal function. Nevertheless, findings from non-(critically) ill individuals with obesity need external validation in (critically) ill individuals as is illustrated by the need for fixed dosing of daptomycin in individuals with obesity and renal function based dose optimization for fluconazole, meropenem, piperacillin and vancomycin[31, 34, 41-45]. For gentamicin dose optimization may be based on both renal function and admission to the ward or ICU[32].

In conclusion, obesity-related changes in exposure to antimicrobial agents can be predicted using studies investigating the influence of body weight on clearance and volume of distribution together with the dosing strategy. Whether the resulting exposure is acceptable depends on the width of the therapeutic window, but also on the sensitivity of the causative pathogen towards the employed antimicrobial agent and penetration of the drug into the site of infection.

The unpredictable effect size of obesity on clearance necessitates early research, similar to renal- and hepatic insufficiency

Nowadays, patients with renal- and hepatic insufficiency are recognized as special patient populations as they are at increased risk to develop drug related toxicity as a result of impaired clearance. Similarly, exposure may be altered in individuals with obesity and the lack of appropriate dose adjustment can put individuals with obesity at the same risk of toxicity. In contrast to individuals with renal- or hepatic impairment, individuals with obesity may also be at risk of therapy failure as illustrated above.

To compare the effect size on clearance of increasing body weight versus renal- and hepatic insufficiency, we summarized the dose adjustments required for individuals with obesity in order to achieve exposure in plasma that is similar to their normal weight counterparts and dose adjustments proposed by the package inserts for renal and hepatic insufficiency for the aforementioned 19 antimicrobial agents (Table 2)[46]. Nevertheless, for some special patient populations additional data on dose adjustment may be available in the field.

For individuals with obesity, dose adjustments are required for 8/19 (42%) antimicrobial agents. Of these eight agents, a dose increase of 25% - 100% is proposed for four antimicrobial agents with a fixed dosing regimen while a dose reduction of up to 36% is proposed for four antimicrobial agents with a weight based dosing regimen. For individuals with renal impairment dose reductions are proposed for 11/19 (58%) of the identified antimicrobial agents. Typical dose adjustments range from 33-95% of the daily dose. For only 2/19 (11%) identified antimicrobial agents a 50% reduced daily maintenance dose is required depending on the severity of hepatic impairment. This low percentage may be explained by the large metabolic capacity of the liver implying that hepatic insufficiency (Child-Pugh class B/C) does not always require dose adjustment for drugs that are subject to hepatic metabolism.

Including individuals with obesity as a special patient population in drug labelling information seems justified as for the 19 evaluated drugs both the number of antimicrobial agents that require dose modification and the corresponding magnitude of the required dose modification are similar to those encountered in individuals with renal impairment and exceed those encountered in individuals with hepatic impairment.

Scenarios for research in individuals with obesity

Regulating bodies recognize the importance of studying drug exposure in individuals with obesity and the current lack of guidance for industry. The Food and Drug Administration (FDA) already propagates enhancement of the diversity of clinical trial populations and the European Medicines Agency (EMA) published a reflection paper emphasizing the importance of studying drug exposure in individuals with obesity[47, 48].

Individuals with obesity are currently often excluded from the early stages of drug research which impedes detecting the influence body weight may or may not have on clearance. As a result, studies identifying the influence of weight on clearance are often conducted during phase IV, after gaining market authorization. In this process, unlocking access to vital information is postponed by several years although this influence could be elucidated through small sample size pharmacokinetic studies. Model Informed Precision Dosing is an important tool for therapy optimization and it has shown its value

in many patient populations for various diseases[49]. In order for these models to provide valid predictions of exposure in individuals with obesity it is of utmost importance to collect data in individuals over a wide weight range.

As a first step, admitting individuals with different classes of obesity to early stages of drug development will yield important information at a pivotal moment as findings can be carried over to later stages of pharmaceutical research. In case body weight shows a strong influence on clearance at an early stage, individualized doses may be administered during subsequent phases of research in order to achieve similar exposure in plasma across different body weights. In contrast, when no influence of body weight on the plasma pharmacokinetics is identified, fixed dosing schedules can be applied in subsequent studies without limits for bodyweight at inclusion of the study.

The clinical population of individuals with obesity may still be heterogeneous with respect to additional factors that may influence clearance such as changes in renal or hepatic function, age or critical illness. As a second step, establishing a platform for sharing and bundling individual data from multi-morbid patients with obesity may potentiate therapy optimization in this special population as collecting data from sufficient multi-morbid individuals may not be feasible in a single center.

We propose to no longer exclude individuals with obesity at any phase of pharmaceutical research and specifically study individuals with (extreme) obesity during drug development. When the influence of weight on clearance is known the moment an antimicrobial agent reaches the market, clinicians are equipped with essential information for therapy optimization.

Conclusion and future perspectives

From our overview, we conclude that obesity has a varying influence on exposure to antimicrobial agents with 7/19 (37%) drugs of which clearance is not significantly increased with bodyweight. Dose adjustments, either a dose increase or a decrease, are required for 8/19 (42%) antimicrobial agents which puts the population of overweight and patients with (morbid) obesity at increased risk of suboptimal exposure. While patients with renal- or hepatic impairment are mostly at risk of overexposure, patients with increased body weight are at double jeopardy as both an increased risk of underexposure and overexposure should be anticipated depending on both the dosing strategy (fixed dose versus mg/kg) and the magnitude of the influence of body weight on clearance as the fold increase in clearance was found to vary between 1.0 and 1.7 for a 70kg vs 140kg individual. Furthermore, therapy optimization is increasingly guided by model-informed decision making while individuals with obesity are not typically studied hence it remains uncertain whether models are fit for purpose in predicting exposure

in individuals with obesity. In order to enable clinicians to individualize antimicrobial therapy in patients with obesity, determining the influence of body weight on exposure to antimicrobial agents should be done at an early stage, ideally from phase I onwards, as it has proven to yield vital information for various antimicrobial agents.

We propose a call to action: patients with (extreme) obesity should be recognized as a special patient population during drug development, especially for antibacterial and antifungal agents given the strong exposure – response relationship.

Disclosures

RB declares no interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead sciences, Merck Sharpe and Dohme Corp., Mundipharma Inc. and Pfizer Inc. All payments were invoiced by the Radboud University Medical Center. PvdL declares membership of the compliance committee of STIZON and is treasurer of the Dutch Working party on Antibiotic Policy (SWAB). The remaining authors have none to declare.

Table 1: Overview of the influence of weight on clearance

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	Ref
Anidulafungin	Moderate increase	Fixed dose	Underexposure	++	Patients with obesity are at risk of underexposure as a result of fixed dosing and increased clearance compared to non-obese individuals	[18]
Caspofungin	Strong increase	Fixed dose	Underexposure	++	Patients with obesity are at risk of underexposure as a result of fixed dosing and increased clearance compared to non-obese individuals	[25]
Fluconazole	Moderate increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in plasma in patients with obesity compared to non-obese individuals.	[10]
Gentamicin	Strong increase	Weight based	Overexposure	++	Total body weight based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. ABW based dosing is often applied in individuals with obesity although this approach shows a trend towards underexposure in individuals with severe morbidity individuals for which a dosing nomogram was proposed.	[16, 32]
Liposomal amphotericin B	No significant increase	Weight based	Overexposure	++	Body weight based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. Doses should be capped for individuals with TBW >100kg when aiming for similar exposure compared to non-obese patients.	[14]
Micafungin	Strong increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in individuals with obesity compared to non-obese individuals. Increased maintenance dose for individuals with TBW>125kg if MIC >0.032mg/L.	[15]
Posaconazole	Moderate increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in plasma in patients with obesity compared to non-obese individuals. Doses should be increased for the treatment of fungal disease for individuals with TBW >140kg.	[12]
Tobramycin	Moderate increase	Weight based	Overexposure	++	Total body weight based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. In obese patients, especially in individuals with good renal function, doses should be optimized based on MDRD and BSA.	[17]

Table 1: Overview of the influence of weight on clearance (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	Ref
Vancomycin	Moderate increase	Weight based	Overexposure	++	Total body weight based dosing leads to similar exposure in individuals with obesity compared to non-obese individuals even though a dose cap is proposed for extremely obese individuals an renal function will determine the optimal dose.	[13]
Cefazolin	No significant increase	Fixed dose	Underexposure	+	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals. Higher dosages may be needed in obese patients when used for surgical prophylaxis because of reported reduced impaired penetration into subcutaneous tissue.	[7]
Ciprofloxacin	No significant increase	Fixed dose	Underexposure	+	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals. Higher dosages may be needed for skin and soft tissue infections in obese patients because of reported decreased tissue penetration.	[6]
Amoxicillin	No significant increase	Fixed dose	-	Neutral	Fixed dosing leads to similar exposure in plasma in obese patients compared to non-obese individuals	[11]
Ceftarolin	Moderate increase	Fixed dose	-	Neutral	Total body weight showed no influence on clearance although Cockcroft-Gault in which weight is used was a predictor. No need for dose adaptation solely based on body weight.	[24]
Daptomycin	Strong increase	Weight based	-	Neutral	Body weight based dosing leads to mildly increased exposure (25-30%) in individuals with obesity compared to non-obese patients which would not lead to safety issues according to the authors.	[23]
Meropenem	Moderate increase	Fixed dose	-	Neutral	Individualized dosing solely based on weight is not necessary. Dose modification is not indicated for most frequently encountered sensitive pathogens (MIC <2mg/L) using a PK/PD target of Time(%) >MIC = 40.	[21]
Moxifloxacin	No significant increase	Fixed dose	-	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	[22]

Table 1: Overview of the influence of weight on clearance (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	Ref
Piperacillin	No significant increase	Fixed dose	-	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	[26]
Tedizolid	Moderate increase	Fixed dose	-	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	[19]
Tigecyclin	No significant increase	Fixed dose	-	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	[20]

The clinical relevance is determined by the combination of both the influence of body weight on clearance and the registered dosing strategy. The clinical relevance is scored neutral if no dose adjustment is needed. "+" is used to indicate differences between individuals with obesity and non-obese patients that do require dose individualization that is not based on differences in clearance from plasma between obese and non-obese patients. "++" is used to indicate differences between individuals with obesity and non-obese patients that require dose individualization based on differences in clearance from plasma.

BSA: body surface area, MDRD: Modification of diet in renal diseases, MIC: Minimal inhibitory concentration, PK/PD: pharmacokinetic/pharmacodynamics, TBW: Total body weight

Table 2: Overview of the proposed dosing recommendations for patients with obesity compared to dose adjustments for renal and hepatic insufficiency

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	Ref
Amoxicillin	No dose adjustment required based on bodyweight.	eGFR 30-10 ml/min: 50% reduced maintenance dose eGFR <10m/min: 75% reduced maintenance dose	No dose adjustment required	[11]
Anidulafungin	25% increased loading- and maintenance dose for TBW >140kg	No dose adjustment required	No dose adjustment required	[18]
Caspofungin	Individuals with obesity will have low caspofungin concentrations despite being on the recommended doses. No dosing advice provided	No dose adjustment required	CP-A: No dose adjustment required CP-B: 50% reduced maintenance dose CP-C: No data	[25]
Cefazolin	No dose adjustment required based on exposure in plasma Surgical prophylaxis: Consider a 50% dose increased for BMI >40kg/m^2	eGFR 40-70 ml/min: 50% reduced daily dose eGFR 20-40 ml/min: 80-85% reduced daily dose eGFR 5-20 ml/min: 90-95% reduced daily dose	No dose adjustment required	[7]
Ceftarolin	No dose adjustment required based on bodyweight.	eGFR 30-50 ml/min: 33% reduced daily dose eGFR 10-30 ml/min: 50% reduced daily dose eGFR <10 ml/min: 66% reduced daily dose	No dose adjustment required	[24]
Ciprofloxacin	No dose adjustment required based on exposure in plasma Skin and soft tissue infection: 120-160kg; increase dosing frequency to 3dd >160kg; increase dosing frequency by to 4dd	30-60 ml/min: 50% reduced daily dose <30 ml/min: 75% reduced daily dose	No dose adjustment required	[6]
Daptomycin	No dose adjustment required based on bodyweight.	eGFR 10-30 ml/min 100% prolonged dosing interval	No dose adjustment required	[23]
Fluconazole	50% increased loading dose for males >140kg	eGFR <50 ml/min 50% reduced maintenance dose	No dose adjustment required	[10]
Gentamicin	Up to 25% dose reduction compared to TBW based dose depending on total body weight	Up to 90% reduced daily dose depending on severity of renal insufficiency, apply TDM	No dose adjustment required	[16, 32]

Table 2: Overview of the proposed dosing recommendations for patients with obesity compared to dose adjustments for renal and hepatic insufficiency (continued)

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	Ref
Liposomal amphotericin B	Cap dosing weight at 100kg	No data	No data	[14]
Meropenem	No dose adjustment required based on bodyweight. Dose adjustment not needed for pathogen with MIC <2mg/L. Higher dosages may be needed for less sensitive pathogens.	eGFR 26-50ml/min 33% reduced daily dose eGFR 10-25ml/min 66% reduced daily dose eGFR <10ml/min 85% reduced daily dose	No dose adjustment required	[21]
Micafugin	Increase maintenance dose by 50-100% if TBW>125kg and MIC 0.016 - 0.032mg/L. Consider alternative therapy for overweight individuals if MIC >0.32mg/L.	No dose adjustment required	CP-A/B: No dose adjustment required CP-C: Insufficient data	[15]
Moxifloxacin	No dose adjustment required based on bodyweight.	No dose adjustment required	Insufficient data	[22]
Piperacillin	No dose adjustment required based on bodyweight.	eGFR 40-20ml/min up to 33% reduced daily dose eGFR <20ml/min 33 – 50% reduced daily dose	No dose adjustment required	[26]
Posaconazole	In case of treatment, increase loading and maintenance dose by 33% for individuals with TBW 140-190kg and by 66% for individuals with TBW >190kg	No dose adjustment required	No dose adjustment required	[12]
Tedizolid	No dose adjustment required based on bodyweight.	No dose adjustment required	No dose adjustment required	[19]
Tigecyclin	No dose adjustment required based on bodyweight.	No dose adjustment required	CP-A/B: No dose adjustment required CP-C: 50% reduced maintenance dose	[20]
Tobramycin	Optimise dose based on MDRD and body surface area nomogram	Up to 80% dose reduction depending on severity of renal insufficiency, apply TDM	No data	[17]

Table 2: Overview of the proposed dosing recommendations for patients with obesity compared to dose adjustments for renal and hepatic insufficiency (continued)

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	Ref
Vancomycin	Daily dose of 35mg/kg (with a maximum of 5500mg/day) for individuals without renal impairment	Apply TDM after the first dose	No dose adjustment required	[13]

The dosing recommendations for patients with obesity are compared to dose adjustments for renal and hepatic insufficiency, as stated in the summary of product characteristics (*)[46]. For some special patient populations additional data on dose adjustment may be available in the field.
BMI: Body mass index, CP: Child Pugh (class A,B,C), eGFR: estimated glomerular filtration rate, MDRD: Modification of diet in renal diseases, MIC: Minimal inhibitory concentration, TBW: Total body weight, TDM: Therapeutic drug monitoring

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Part III

Antimicrobial pharmacokinetics in hospitalized patients with multimorbidity

CHAPTER 5

5

Pooled population pharmacokinetics analysis and dose recommendations for ciprofloxacin in Intensive Care Unit patients with obesity

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Abstract

Introduction: Recent studies have explored the influence of obesity and of critical illness on ciprofloxacin pharmacokinetics. However, variation across the subpopulation of individuals with obesity admitted to the ICU with varying renal function remains unexamined. This study aims to characterize ciprofloxacin pharmacokinetics in ICU patients with obesity and provide dose recommendations for this special population.

Methods: Individual patient data of 34 ICU patients with obesity (BMI >30kg/m^2) from 4 studies evaluating ciprofloxacin pharmacokinetics in ICU patients were pooled and combined with data from a study involving 10 individuals with obesity undergoing bariatric surgery. All samples were collected after intravenous administration. Non-linear mixed effects modelling and simulation were used to develop a population pharmacokinetic model and describe ciprofloxacin exposure in plasma. Model based dose evaluations were performed using a PK/PD target of AUC/MIC>125.

Results: The data from patients with BMI ranging from 30.2 – 58.1 were best described by a two-compartment model with first order elimination and a proportional error model. Inclusion of CKD-EPI as a covariate on clearance reduced inter-individual variability from 57.3% to 38.5% ($p<0.001$). Neither body weight nor ICU admission significantly influenced clearance or volume of distribution.

Conclusions: Renal function is a viable predictor for ciprofloxacin clearance in ICU patients with obesity, while critical illness and body weight do not significantly alter clearance. As such body weight and critical illness do not need to be accounted for when dosing ciprofloxacin in ICU patients with obesity. Individuals with CKD-EPI >60ml/min/1.73m^2 may require higher dosages for the treatment of pathogens with MIC ≥0.25mg/L.

Introduction

Ciprofloxacin is a fluoroquinolone used for empirical and targeted therapy of infections caused by a wide range of gram-negative pathogens in intensive care unit (ICU) patients. It is cleared by glomerular filtration, tubular secretion, trans-epithelial intestinal secretion and hepatic metabolism[1,2]. Enterobacterales, with minimal inhibitory concentrations (MIC) ranging from 0.064 – 0.25 mg/L are commonly targeted with ciprofloxacin[1]. The pharmacokinetic/pharmacodynamic (PK/PD) index that correlates best with clinical – and microbiological cure is the area under the curve (AUC) divided by the MIC[3]. There is a growing body of evidence that standard ciprofloxacin dosing regimens do not result in sufficient exposure to achieve a PK/PD target of AUC/MIC>125, especially for pathogens with MIC of 0.5 mg/L like P. *Aeruginosa*[4-7]. Guidelines currently recommend a dosing regimen of 400 mg q8h in ICU patients with extension of the dose interval for individuals with impaired renal function, with a maximum daily dose being 1600 mg[1,2,8].

Ciprofloxacin clearance and volume of distribution were found to be uninfluenced by body weight in (morbidly) obese individuals with body weights up to 212 kg undergoing bariatric surgery[9]. Previous studies in patients admitted to the ICU however show that renal function was associated with ciprofloxacin clearance albeit with considerable remaining variability[4-7,10]. It is therefore likely that dose modification is needed in obese ICU patients with varying renal function. The objective of this study was to characterize ciprofloxacin pharmacokinetics in ICU patients with obesity and varying renal function and explore dose optimization for this special population.

Materials & Methods

Patients and data

Data of total drug concentrations obtained in ICU patients with obesity (BMI ≥30kg/m2) treated with intravenous ciprofloxacin from 4 cohorts, all from university hospitals, were pooled[4-7]. Patients were excluded if they received renal replacement therapy or had Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) ≤20ml/min (without renal replacement therapy). Cohort 1 was a prospective observational study with 12 obese participants (147 samples) at Radboud University hospital (Nijmegen, the Netherlands)[6], Cohort 2 was a prospective observational study with 10 patients (86 samples) with obesity at Amsterdam UMC (Amsterdam, the Netherlands)[7], Cohort 3 was a prospective observational cohort with 4 participants (20 samples) with obesity at Erasmus University Hospital (Rotterdam, the Netherlands, NTR5632)[5], Cohort 4 was a prospective observational cohort with 8 participants (44 samples) with obesity at Copenhagen university hospital (Rigshospitalet, (Copenhagen, Denmark,

NCT02240277)[4]. The patients' data were simultaneously modelled with data from a cohort of 10 obese individuals undergoing bariatric surgery (106 samples) who received intravenous ciprofloxacin (NTR6058)[9].

Data on patient characteristics (sex, age, measures of body weight, height, BMI, serum creatinine, SOFA score and length of ICU stay at initiation of therapy) and ciprofloxacin treatment (dose, time and rate of administration) were collected. Estimated glomerular filtration rate was calculated using CKD-EPI, Modification of Diet in Renal Diseases (MDRD) and Cockcroft-Gault (CG)[11-13]. CKD-EPI and MDRD were de-indexed for body surface area (BSA) by multiplying the respective values by BSA/1.73. BSA was calculated using the Du Bois/ Du Bois formula[14].

Ethics

The local medical ethical committee Nijmegen provided a waiver for informed consent for participants in cohort 1 due to the observational nature of the study6. Participants in cohort 2 – 4 and the control group gave written informed consent for inclusion in the original studies[4,5,7,9]. All studies were conducted according to the Good Clinical Practices and the declaration of Helsinki[15,16]. Before sharing, all previously collected data was anonymized by the corresponding authors of the respective studies with ethics approval for data sharing provided where required in the local jurisdiction.

Pharmacokinetic analysis

All concentration-time data from the 4 cohorts and the control group were simultaneously analyzed by non-linear effects modelling using first-order conditional estimation with interaction (NONMEM; v7.4.0)[17].

A one- and two-compartment model with first-order elimination was tested to describe ciprofloxacin pharmacokinetics. Additive, proportional and combined residual error models were evaluated. Log-normal distribution of interindividual variability (IIV) was assumed. In the covariate analysis associations between model parameters and potential covariates (ICU admission, CKD-EPI, CKD-EPI$_{de\text{-}indexed}$, MDRD, MDRD$_{de\text{-}indexed}$, Sex, Age, TBW, LBW, ABW) were tested. Continuous covariates were implemented in the model using Equation (1) and (2), respectively. P_i and P_p represent the individual and population parameter estimates, Y represents the exponent for a power function and Z represents the slope of a linear covariate relationship. For dichotomous covariates different parameters were estimated for the respective subgroup. If multiple creatinine observations were available for an individual, renal function estimators were assessed as a time varying covariate with linear interpolation. Time varying covariates were analyzed by plotting conditional weighted residual (CWRES) versus the time varying covariate. Inter occasion variability was tested on clearance as this parameter is most

influential on ciprofloxacin exposure in plasma. An occasion was defined as 24 hours assuming dose adjustments are made on a daily basis.

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^Y \quad (1)$$

$$P_i = P_p \times \left(1 + Z \times (COV - COV_{standard})\right) \quad (2)$$

During model development, changes in objective function value (OFV), reduction in IIV and residual error, Goodness of Fit (GOF) and CWRES plots split for quantiles of covariates and diagnostic plots were used to compare models. Internal model validation was done using prediction corrected visual predictive check (pcVPC), normalized prediction distribution errors (NPDE) plots, GOF-plots, CWRES-plots and sampling importance resampling (SIR).

Exposure in plasma was simulated for 20.000 virtual ICU patients with obesity based on the final model. CKD-EPI was uniformly distributed between 20 and 120 ml/min/1.73m^2. The probability of target attainment (PTA) in the first 24 hours after initiation of therapy for pathogens with minimal inhibitory concentration (MIC) ranging from 0.064mg/L to 0.5mg/L was simulated using a pharmacokinetic/pharmacodynamic target of AUC/MIC>125, a PTA of 90% was considered acceptable since exposure is evaluated in the first 24 hours of therapy and consequently plasma concentration may increase during subsequent days of therapy[1,3]. Exposure for six different dosing regimens was investigated with daily intravenous doses ranging from 400 – 2400mg.

Results

Population characteristics

We included 44 individuals with obesity of which 34 were admitted to the ICU and 10 in the control group. We analyzed 403 samples of which 297 and 106 were collected in the ICU patients and the control group, respectively. In the ICU population 106 samples (36%), 125 samples (42%), 33 samples (11%) and 33 samples (11%) were collected on day 1, 2, 3 and >day 3 of initiation of ciprofloxacin therapy, respectively. Length of ICU stay (LOS) and SOFA score median (IQR) were 2 (1 – 3.5) days and 7.5 (6 – 10.5), respectively. Weight and renal function (assessed by CKD-EPI) ranged from 75 – 167 kg and 21-115 ml/min/1.73m^2 in the ICU patients and from 107 – 212 kg and 72 – 115ml/min/1.73m^2 in the control group. Further details on population characteristics are shown in Table 1. SOFA score was available for 28 patients (82%), all other data was complete for all patients.

Table 1: Baseline population demographics

	ICU patients with obesity (n=34)	Control group with obesity (n=10)
Age	58 (33 – 80)	50 (36 – 57)
Sex, male, n(%)	22 (65%)	5 (50%)
Weight (kg)	110 (75 – 167)	139 (107 – 212)
Lean body weight (kg)	69 (42 – 95)	67 (52 – 102)
Body surface area (m^2)	2.3 (1.7 – 2.8)	2.5 (2.1 – 3.2)
Body mass index (kg/m^2)	35.5 (30.2 – 54.5)	44.9 (38.5 – 58.1)
Number of days at ICU at initiation of therapy (median, IQR)	2 (1 – 3.5)	n.a.
SOFA score at initiation of therapy (median, IQR)[a]	7.5 (6 – 10.5)	n.a.
Serum creatinine (µmol/L)	119 (51 – 298)	76 (56 – 90)
CKD-EPI ($ml/min/1.73m^2$)	54 (21 – 115)	94 (72 – 115)
De-indexed CKD-EPI (ml/min)	75 (23 – 163)	134 (86 – 184)
MDRD ($ml/min/1.73m^2$)	49 (19 – 145)	86 (65 – 119)
De-indexed MDRD ($ml/min/1.73m^2$)	66 (22 – 108)	123 (78 – 191)
No of samples	297	106
Average no of samples per individual	8.7	10.6

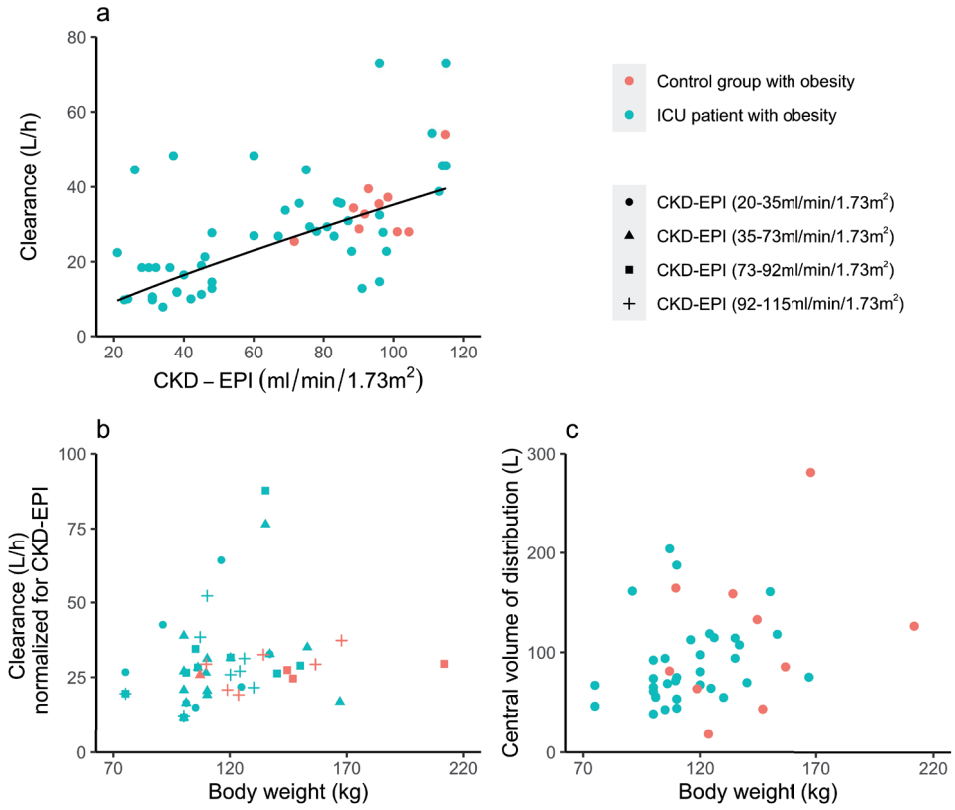
Data are shown as median (range) unless otherwise specified. Renal function was recorded at baseline. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, ICU: Intensive care unit. IQR: Interquartile range. MRD: Modification of diet in renal disease, SOFA: Sequential Organ Failure Assessment.
[a] based on data from 28 patients (82%)

Pharmacokinetic analysis

The data were best described by a two-compartment model with first-order elimination and a proportional error model. CKD-EPI was identified as a significant covariate on ciprofloxacin clearance as IIV reduced from 57.1% to 38.5% (dOFV -66.4, $p<0.001$). Individual values for clearance versus CKD-EPI for the base model are shown in Figure 1a. The different renal function estimators yielded a similar reduction of OFV and IIV on clearance, moreover diagnostic plots did not show pronounced differences. We implemented CKD-EPI in the final pharmacokinetic model as this parameter is most widely used in clinical practice. Our model could not be improved by inclusion of bodyweight as a covariate on clearance (exponent 0.136, dOFV -0.2, $p>0.05$, no improvement in GOF) or volume of distribution (exponent 0.8, dOFV -1.7, $p>0.05$, no improvement in GOF).

The GOF-plot, pcVPC (split for quantiles of CKD-EPI) and NPDE for the final model and diagnostic plots for renal function estimators of the base model are shown in Figure S1 – S4.

Figure 1



The individual values for clearance versus renal function (CKD-EPI) from the base model are shown in panel a. The black line indicates the covariate relation as implemented in the final model.
Individual values for clearance and volume of distribution versus total body weight for the final model are shown in panel b and c and indicate no statistically significant trend with bodyweight. The individual values for clearance in panel b are normalized for CKD-EPI at baseline (by $CL_{norm,\,i} = CL_i / (CKD_i$, *baseline* $/73)^{0.833}$*). The shape of the datapoints in panel b indicates the quantile of renal function at baseline.*

The model could not be improved by including a measure of bodyweight or (critical) illness (ICU admission, SOFA score, length of ICU stay) as a covariate on clearance or volume of distribution. Individual values of clearance (normalized for CKD-EPI) and volume of distribution versus total body weight for the final model are shown in Figure 1b and 1c illustrating there are no statistically significant trends with increasing body weight or ICU admission. The parameter estimates and SIR 95% confidence interval for the final model are presented in table 2. The model code and template for the dataset are provided in the supplementary material.

Table 2: Parameter estimates of the population pharmacokinetic model

Parameter	Base model (%RSE)	Final model (%RSE)	SIR 95% CI based on the final iteration of 5000 samples/ 1000 resamples
Fixed effects			
CL (L/h)	24.3 (8.3)		
$CL = CL_{CKD\text{-}EPI} * (CKD/73)^{X}$			
$CL_{CKD\text{-}EPI}$		27.1 (5.2)	24.5 – 29.9
X		0.833 (15.8)	0.616 – 1.05
V_c (L)	81.7 (14.4)	82.5 (14.1)	64.6 – 102.0
V_p (L)	121 (8.5)	115 (8.6)	98.7 – 133.5
Q (L/h)	60.2 (14.8)	59.1 (19)	51.7 – 70.9
Interindividual variability (%)[a,b]			
CL	57.1 (10.3)	38.5 (11.9)	31.3 – 45.2
V_c	64 (19.7)	65.9 (17.7)	42.1 – 76.6
V_p	44.8 (18.7)	38.3 (16.3)	27.0 – 49.0
Covariance $(CL/V_c)^c$		0.132	0.07 – 0.21
Residual variability (%)			
Proportional error [d]	16.8 (8.3)	16.3 (8.6)	14.9 – 18.1
OFV	-428.0	-494.4	

The parameter estimates are shown with the relative standard error. CI confidence interval, CL systemic clearance, CKD-EPI estimated glomerular function rate (ml/min/1.73m^2), OFV objective function value, Q intercompartmental clearance, RSE residual standard error, SIR sampling importance resampling, V_c central volume of distribution, V_p peripheral volume of distribution.

[a]: η-shrinkage of the final model: CL 3%, V_c 14%, V_p 28%

[b]: Calculated as: $\sqrt{(e^{\omega^2} - 1)}$

[c]: Correlation coefficient (RSE): 59.1% (18.7%)

[d]: ε-shrinkage: 11%

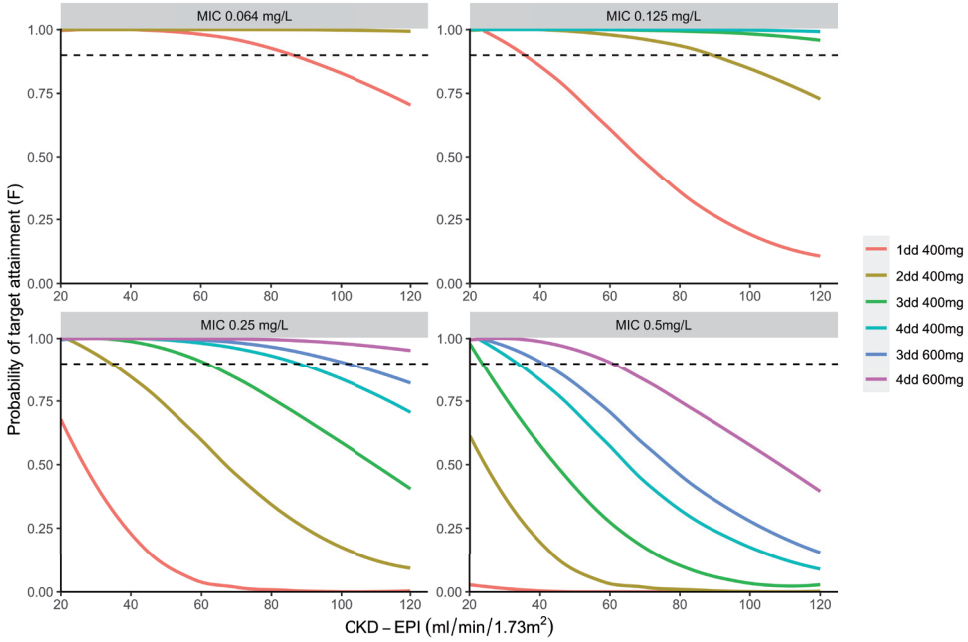
Model based dose evaluations

The probability of target attainment versus renal function for various dosing regimens split for pathogens with MIC ranging from 0.064mg/L to 0.5mg/L is shown in figure 2. This figure illustrates that the standard dosing regimen of ciprofloxacin 400mg q8h for individuals with CKD-EPI >30ml/min/1.73m^2 and with an increased dose interval of q12h for individuals with CKD-EPI <30 ml/min/1.73m^2 provides exposure in ICU patients with obesity that is sufficient to reach PTA >90% for all pathogens with MIC 0.064 – 0.125mg/L. For the treatment of pathogens with MIC 0.25mg/L, individuals with CKD-EPI >45ml/min/1.73m^2 fail to achieve this PK/PD target on day 1 of therapy although this target may be reached on day 2 of therapy as shown in Figure S5. A dosing regimen of

400mg ciprofloxacin q6h may provide PTA>90% for individuals with CKD-EPI 60 – 90ml/min/1.73m^2.

To evaluate safety of the simulated dosing regimens, the median and 90th percentile exposure versus renal function for the respective dosing regimens are shown in Figure S6, in which $AUC_{24\text{-}48h}$ is shown as highest exposure that will be attained during therapy. The median exposures for individuals with CKD-EPI 20-30ml/min/1.73m^2 receiving 400mg q12h, CKD-EPI 30-60ml/min/1.73m2 receiving 400mg q8h, and CKD-EPI 60-90 ml/min/1.73m2 receiving 400mg q6h are similar with 57 – 73 mg*h/L, 53 – 85 mg*h/L and 52 – 72 mg*h/L, respectively.

Figure 2



The probability of target attainment on the first day of therapy (using a target of AUC/MIC>125) versus renal function for various intravenous ciprofloxacin dosing regimens split for minimal inhibitory concentration (MIC) of the causative pathogen. The dashed line represents a target probability of target attainment of 90%.

Discussion

In this pooled pharmacokinetic analysis we show that CKD-EPI was the most important parameter for the prediction of ciprofloxacin clearance in individuals with obesity admitted to the ICU. Interestingly, both body weight and admission to the ICU did not influence the estimation of clearance and volume of distribution in this study and therefore dose adjustment solely based on body weight in ICU patients with obesity is not needed. Model based dose evaluation shows that current dosing regimens may not ensure target attainment for the treatment of pathogens with MIC ≥0.25mg/L in individuals with renal function >60 ml/min/1.73m^2.

To our knowledge this is the first study to evaluate ciprofloxacin exposure in a large cohort of individuals with obesity admitted to the ICU. A strength of our study is the use of pooled data from 4 university hospital ICU's in 2 countries which is an approach that could be used more widely, facilitating research in individuals with obesity in the ICU. The inclusion of a wide range in body weight and renal function allows discrimination of the predictive performance of renal function estimators at extreme bodyweight. In our study population of ICU patients with obesity the difference in predictive performance of MDRD and CKD-EPI was minimal and therefore the CKD-EPI was retained in the final model as this estimator of glomerular filtration rate is used most frequently in clinical practice. Our finding that clearance is correlated with renal function is consistent with previous studies on ciprofloxacin pharmacokinetics in the general ICU population[4,6,7].

ICU patients may initially be hemodynamically unstable, receive aggressive fluid resuscitation, have augmented renal clearance or acute kidney injury[18]. As a result, the potential influence of ICU admission on ciprofloxacin pharmacokinetics in individuals with obesity is expected to be most severe in the first 2 days of therapy. In our study 78% of all PK observation in ICU patients were collected within this critical period which is an important strength. In our study, ICU admission, SOFA score and Length of Stay at the ICU were not predictive for clearance although some patients with obesity admitted to the ICU showed high clearance despite a relatively low CKD-EPI. A possible explanation may be that creatinine is a late marker for changes in renal function. Initially, an increase in renal clearance may not yet be reflected in low serum creatinine.

Our study, which aimed at capturing the influence of body weight on ciprofloxacin pharmacokinetics in ICU patients with obesity, does not show improvement of the model after inclusion of body weight as a covariate. Therefore, fixed dosing in ICU patients with obesity with a dose modification based on renal function seems appropriate although previous studies on ciprofloxacin PK in ICU patients covering a narrower weight range assumed an influence of weight on clearance and volume of distribution by applying

a-priori allometric scaling which may result in higher dosages in ICU patients with obesity[6,7]. Moreover, a loading dose is not warranted in individuals with obesity as body weight was not associated with alterations in volume of distribution. Previously, Roberts *et al.* identified an association between body weight and volume of distribution in a study on ciprofloxacin pharmacokinetics in patients with septic shock for which a power-function with an exponent as low as 0.75 was found[4]. The finding that body weight is not correlated with clearance or volume of distribution in patients with obesity admitted to the ICU is consistent with our previous study in otherwise healthy individuals with obesity undergoing bariatric surgery[9].

Some limitations may apply to our results as individuals with obesity and severely impaired renal function (CKD-EPI <20ml/min/1.73m^2) or on renal replacement therapy were excluded from our study. Therefore, our results cannot be extrapolated to this population. Also, data on SOFA score are not complete which may hinder judgement of external validity of our results although SOFA score and length of ICU stay versus CWRES plots did not show any significant trend.

Ciprofloxacin treatment in patients admitted to the ICU usually consists of ciprofloxacin 400mg q8h with an increase in dosing interval to q12h for individuals with CKD-EPI <30ml/min/1.73m^2. Using this dosing approach, PTA is sufficient for the treatment of pathogens with MIC <0.25mg/L irrespective of renal function, body weight and ICU admittance. The results of our study do show that treatment of pathogens with MIC ≥0.25mg/L remains challenging, especially for individuals with CKD-EPI >60ml/min/1.73m^2 as increasingly higher dosages may be needed to achieve target attainment while experience with doses beyond 400mg q8h is limited. A need for ciprofloxacin doses beyond 1200mg/day in critically ill patients on the first day of therapy using a cut-off MIC of 1.0mg/L as was demonstrated by Roggeveen *et al.*[19]. The upper limit of safety for ciprofloxacin exposure is not well defined and it thus remains unclear if dosages beyond the current guidelines, which may be needed to achieve the PK/PD target for the treatment of pathogens with MIC ≥0.25mg/L in patients with CKD-EPI >60ml/min/1.73m^2 can be applied safely. Daily doses of up to 2000mg have been applied in children with cystic fibrosis although exposure remained relatively low as a result of increased clearance in this population[20].

A prospective clinical study testing renal function based dose individualization is needed to elucidate if doses beyond 1200mg/day lead to improved clinical outcomes in individuals with CKD-EPI >60ml/min/1.73m^2 as the AUC/MIC>125 PK/PD target is not extensively investigated.

Conclusions

Ciprofloxacin plasma concentration in individuals with obesity may be influenced by renal function but not by body weight or ICU admission. For pathogens with MIC 0.064mg/L – 0.125mg/L target attainment can be achieved with daily doses of 1200mg. The currently applied dosing regimens may not result in sufficient exposure for the treatment of pathogens with MIC ≥0.25mg/L in individuals with CKD-EPI >60ml/min/1.73m^2.

Disclosures

R.J.M.B. declares no interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead sciences, Merck Sharpe and Dohme Corp., Mundipharma Inc. and Pfizer Inc. All payments were invoiced by the Radboud University Medical Center. P.D.v.d.L. declares membership of the compliance committee of STIZON and is treasurer of the Dutch Working party on Antibiotic Policy (SWAB). J.A.R. would like to acknowledge funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP2007007) and an Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship.

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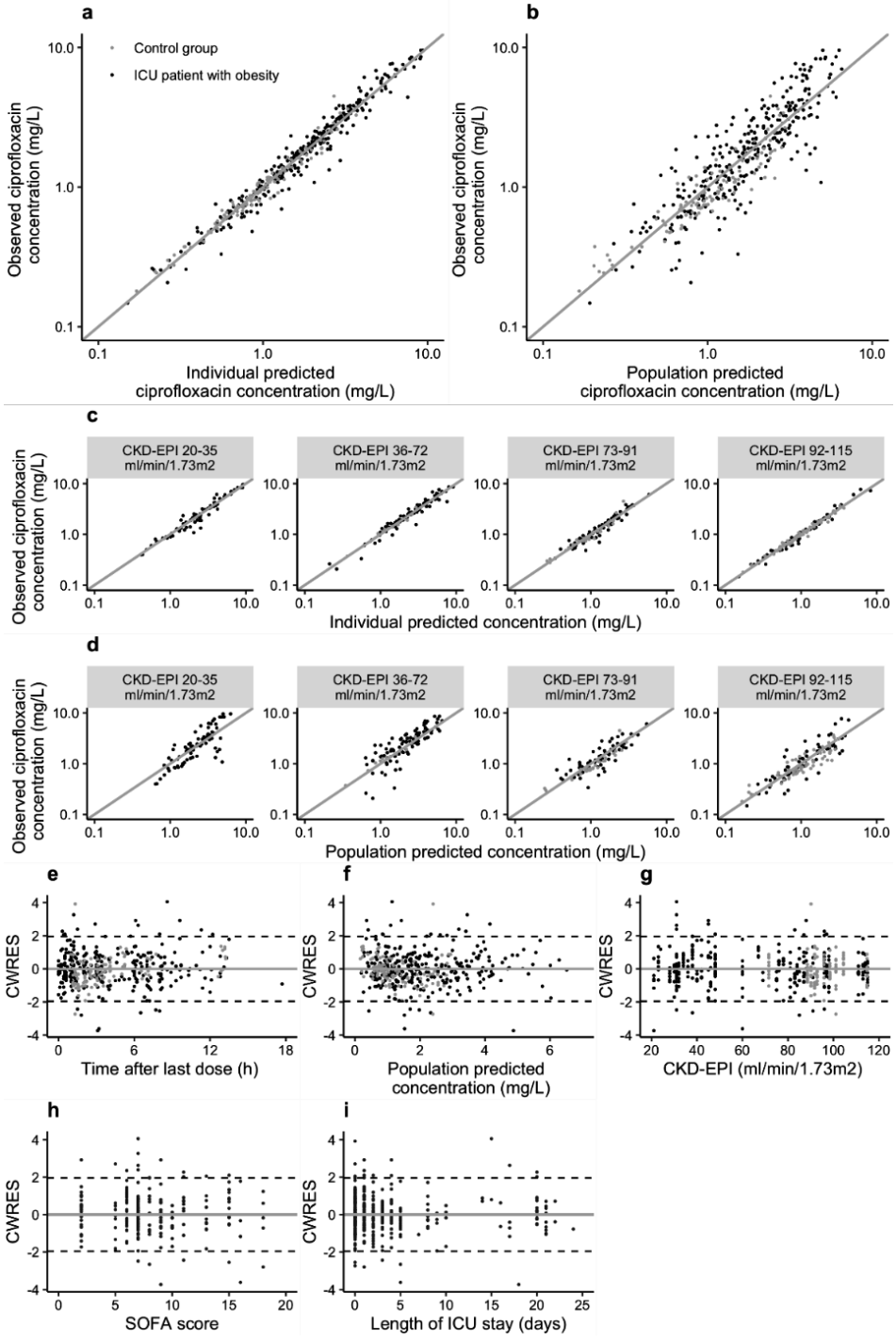
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Supplementary material

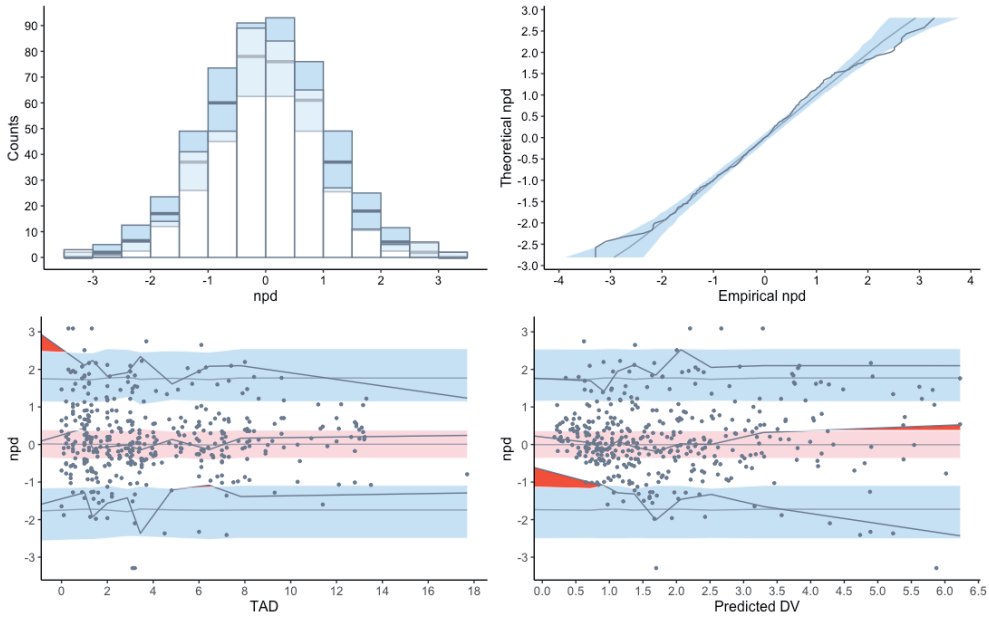
Figure S1: Diagnostic plots for the final pharmacokinetic model



Diagnostic plots of the final model for critically ill individuals with obesity (black dots) and the obese control group (grey dots). The grey line represents the line of identity and the dashed lines represent the 1.96, – 1.96 interval indicating the range within which 95% of the observations are expected to fall. CWRES: conditional weighted residuals CKD-EPI: chronic kidney disease epidemiology collaboration.

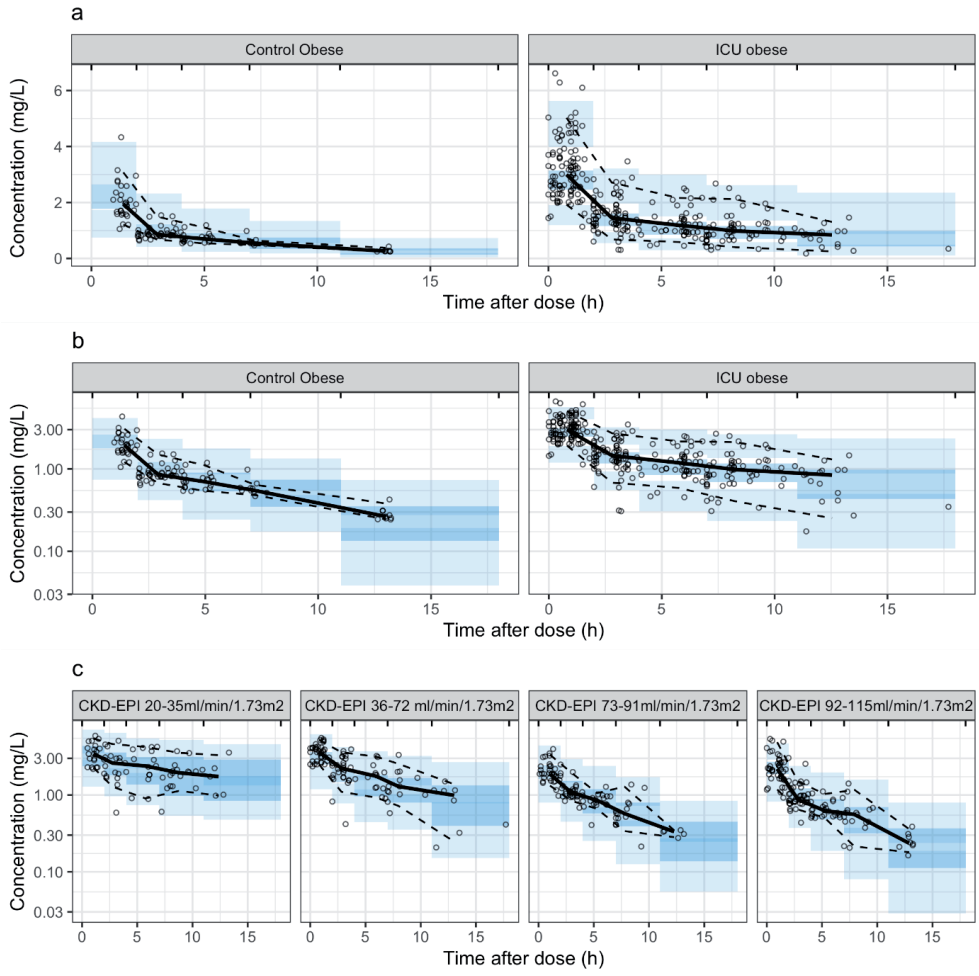
a) *Individual predicted concentration vs observed ciprofloxacin concentration*
b) *Population predicted concentration vs observed ciprofloxacin concentration*
c) *Individual predicted concentration vs observed ciprofloxacin concentration split for CKD*
d) *Population predicted concentration vs observed ciprofloxacin concentration split for CKD*
e) *Time after last dose versus CWRES*
f) *Population predicted ciprofloxacin concentrations versus CWRES*
g) *Renal function (estimated by CKD-EPI) versus CWRES*
h) *Sequential organ failure assessment (SOFA) score versus CWRES*
i) *Length of ICU stay (days) at start of therapy versus CWRES*

Figure S2: Normalized prediction distribution error of the final pharmacokinetic model



The NPDE shows no model misspecification as the data overlap the theoretical histogram (upper left panel), data points in the QQ plot follow the theoretical and are within the 95% confidence interval (upper right panel). Data points are scattered around the null line without a significant trend with time after dose (TAD) or predicted concentration (lower left and right panels).

Figure S3: Prediction corrected visual predictive check of the final pharmacokinetic model



Prediction corrected visual predictive check of the final model

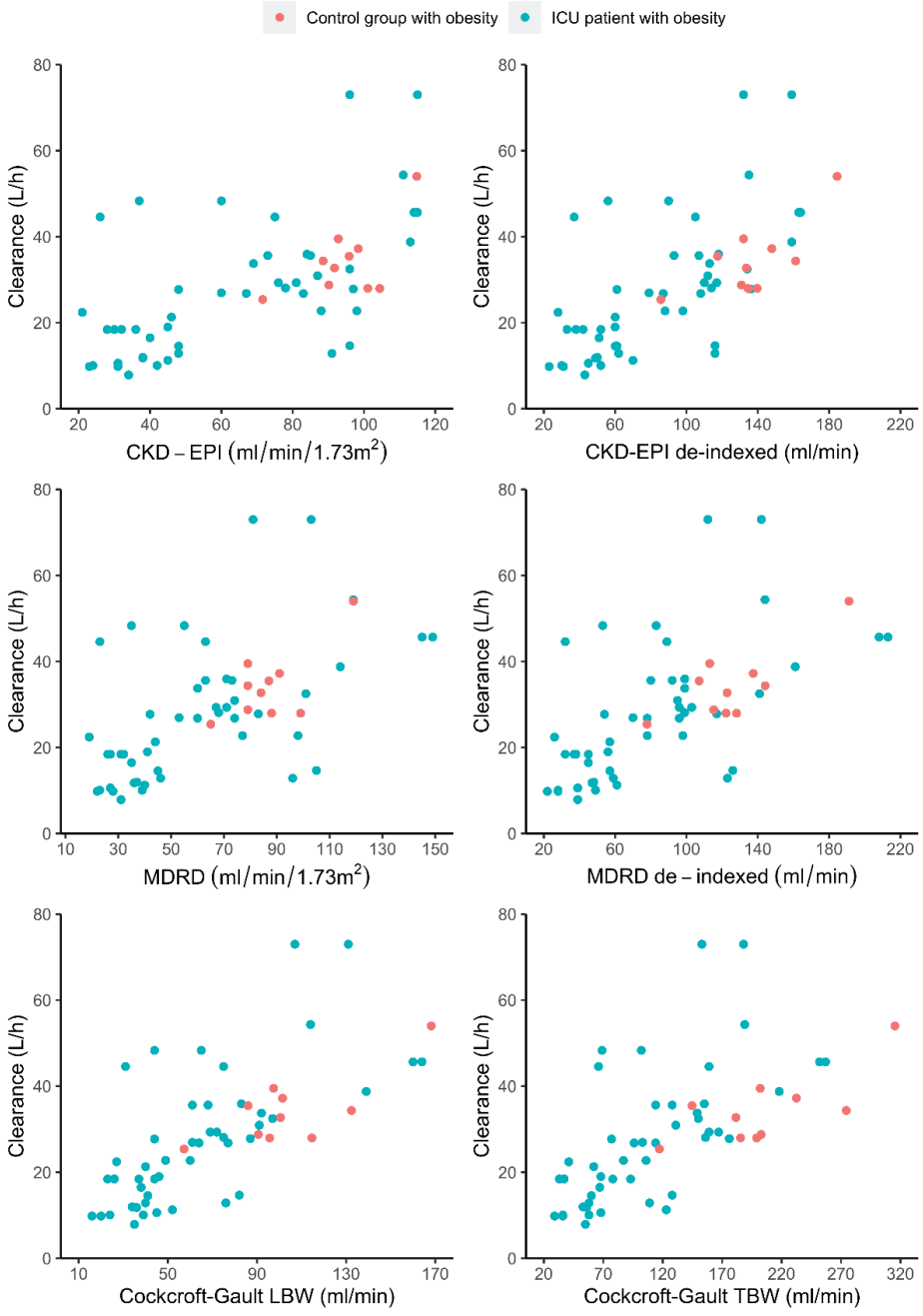
a) *stratified by subgroup on a linear scale*

b) *stratified by subgroup on a logarithmic scale*

c) *stratified by CKD-EPI on a logarithmic scale*

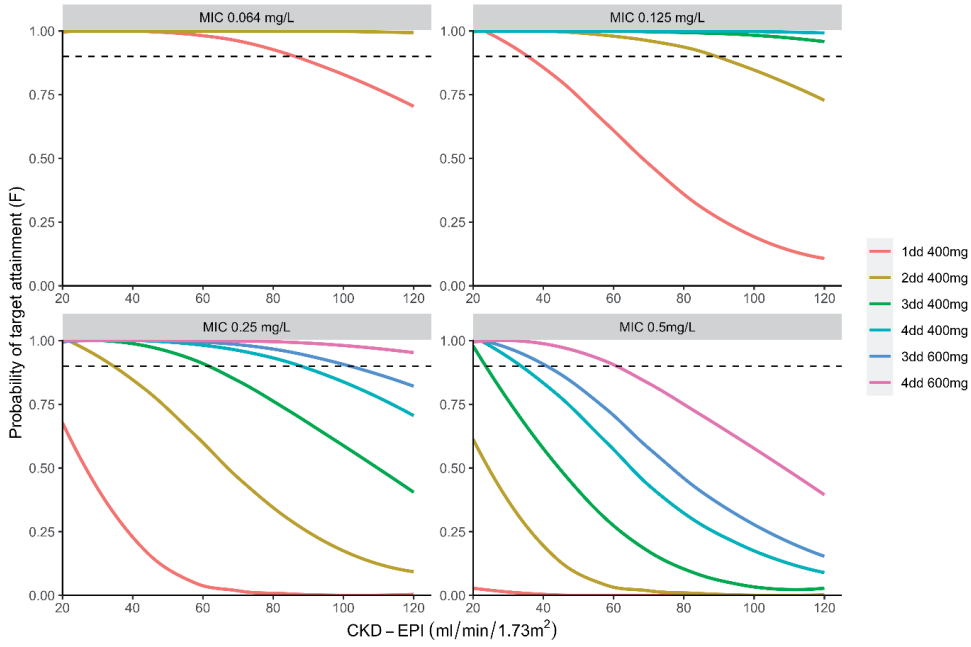
The observed data are shown as circles with the median and 2.5th and 97.5th percentile of the observed data shown as a solid black line and the upper and lower dashed lines, respecitvely. The blue areas represent the 95% confidence interval of the simulated median (dark blue) and 5th and 95th percentile (light blue) of the simulated concentrations based on 1000 simulations of the original dataset. Vertical lines at the top of the panels represent the bins.

Figure S4: Renal function estimators versus clearance for the base model



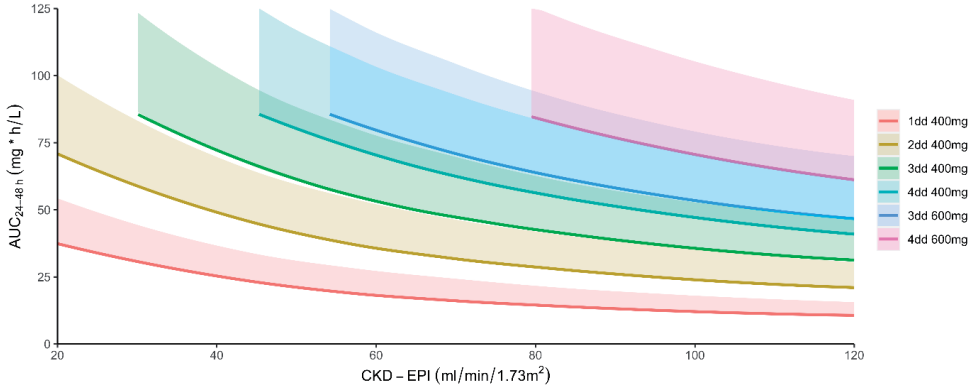
Mean individual values for clearance versus renal function estimators for the base model showing similar correlation for the renal function estimators. Patients admitted to the intensive care unit and the control group are shown in teal and red, respectively.

Figure S5: Probability of target attainment after the first day of therapy



The probability of target attainment after the first day of therapy (using a target of AUC/MIC>125) versus renal function for various intravenous ciprofloxacin dosing regimens split for minimal inhibitory concentration (MIC) of the causative pathogen. The dashed line represents a target probability of target attainment of 90%.

Figure S6: Median and 90th percentile exposure for the simulated dosing regimens for varying renal function



*Exposure versus renal function for the ciprofloxacin dosing regimens after the first day of therapy ($AUC_{24\text{-}48h}$) is shown as median (line) and median-90th percentile (shaded area). The shaded area is only plotted if the 90th percentile AUC is <125 mg*h/L which corresponds with the highest exposure reached after 3dd 400mg in an individual with CKD-EPI 30ml/min/1.72m^2.*
This reference exposure is not exceeded in ICU patients with obesity with CKD-EPI >46ml/min/1.73m^2, >55ml/min/1.73m^2 and >80ml/min/1.72m^2 after administration of 4dd 400mg, 3dd 600mg and 4dd 600mg, respectively.

NONMEM control stream for the final model

```
;; 1. Based on: run01
;; 2. Description: Ciprofloxacin PK in ICU patients with obesity
;; x1. Author: Koen van Rhee
;; 3. Label: Ciprofloxacin ICU
$PROBLEM Ciprofloxacin ICU
$INPUT ID TIME AMT RATE DV CMT EVID MDV CKD ICU
$DATA dataset.csv IGNORE=@

$SUBROUTINE ADVAN6 TOL9
$MODEL COMP=(CENT) COMP=(PERI)
$PK

; DISPOSITION MODEL
TVCL = THETA(1) * ((CKD/73)**THETA(5))
CL = TVCL * EXP(ETA(1))          ; CLEARANCE
V1 = THETA(2) * EXP(ETA(2))      ; CENTRAL VOLUME OF DISTRIBUTION
Q = THETA(3) * EXP(ETA(3))       ; INTERCOMPARTIMENTAL CLEARANCE
```

```
TVV2= THETA(4)
V2 = TVV2 * EXP(ETA(4))              ; PERIPHERAL VOLUME OF DISTRIBUTION
K12 = Q/V1
K21 = Q/V2
K10 = CL/V1                          ; ELIMINATION RATE CONSTANT

S1 = V1
S2 = V2

$DES
DADT(1)=-K12*A(1)+K21*A(2)-K10*A(1)
DADT(2)=K12*A(1)-K21*A(2)

$ERROR
IPRED = A(1)/S1 ; individual prediction
Y = IPRED + IPRED*EPS(1) + EPS(2)
IRES = DV-IPRED

$THETA
 27.1 ; CL
 82.5 ; V1
 59.1 ; Q
 115 ; V2
 0.833 ; CKD ON CL

$OMEGA BLOCK(2)
 0.138               ; IIV CL
 0.132 0.361         ; IIV V1
$OMEGA
 0 FIX               ; IIV Q
 0.137               ; IIV V2

$SIGMA
 0.0262 ; Proportional error PK
 0 FIX ; Additional error PK
$ESTIMATION METHOD=1 INTER MAXEVAL=999 NOABORT SIGL=9 NSIG=3 PRINT=5
POSTHOC
$COVARIANCE PRINT=E
$TABLE ID TIME DV MDV EVID IPRED ETAS(1:LAST) CWRES ONEHEADER NOPRINT
FILE=sdtab01
```

CHAPTER 6

6

Impact of mucositis on oral bioavailability and systemic exposure of ciprofloxacin gram-negative infection prophylaxis in patients with hematological malignancies

Koen P. van Rhee, Suzanne L. de Vroom, Reinier M. van Hest, Paul D. van der linden, Sanne H. Tonino, Eva Molendijk, Ron A. A. Mathôt, Nicole M.A. Blijlevens, Catherijne A.J. Knibbe, Roger J.M. Brüggemann, Suzanne E. Geerlings



Abstract

Introduction: Patients with hematological malignancies frequently endure neutropenia and gastro intestinal (GI)-mucositis after high-dose chemotherapy. In these patients, ciprofloxacin is used for gram-negative infection prophylaxis.

We investigate ciprofloxacin pharmacokinetics after oral administration in patients with hematological malignancies and explore the impact of GI-mucositis on oral bioavailability and clearance in order to assure adequate systemic exposure.

Methods: Adult hematological patients from two Dutch University Medical Centers received 500 mg twice daily oral ciprofloxacin for gram negative prophylaxis. The ciprofloxacin plasma concentrations were collected at various timepoints after oral ciprofloxacin administration and at various days after completion of chemotherapy. Data obtained after oral and intravenous ciprofloxacin administration in 28 healthy volunteers without mucositis served as a control group (391 samples). For hematological patients the degree of GI-mucositis was assessed using the Daily Gut Score (DGS), plasma citrulline and albumin. Data were analyzed by non-linear mixed-effects modelling.

Results: In total, 250 blood samples were collected in 47 patients with a wide variety of hematological malignancies between 0-30 days after start of chemotherapy. Mucositis was generally mild (DGS: 1 (1-1) and citrulline 16 µmol/L (12-23) (median, (IQR)). The time to C_{max} was slower in hematological patients compared to healthy volunteers although no association with the degree of mucositis (defined as DGS or citrulline) could be identified. Ciprofloxacin bioavailability and clearance were 60% and 33.2 L/h, respectively.

Conclusion: This study supports oral dosing of ciprofloxacin as gram negative infection prophylaxis in hematological patients with mild to moderate mucositis capable of oral intake.

INTRODUCTION

Fluoroquinolone prophylaxis reduces the relative risk of infection-related mortality in neutropenic patients with hematological malignancies by 68% while adverse effects and development of resistance are not significantly increased.[1-4] Of the fluoroquinolones, ciprofloxacin is the most frequently prescribed. It is typically administered orally in dosages of 500 mg twice daily and is rapidly and well absorbed from the gastro-intestinal tract in healthy volunteers with a bioavailability of approximately 60-80%. Ciprofloxacin is subject to glomerular filtration, tubular secretion, trans-epithelial intestinal secretion and hepatic metabolism.[5]

Patients with hematological malignancies treated with high dose chemotherapy often encounter mucosal disruption of the gastrointestinal (GI) tract (i.e. GI-mucositis).[6,7] Mucositis affects oral absorption unpredictably in patients with hematological malignancies; for example, posaconazole bioavailability is reduced while isavuconazole bioavailability remains unaltered.[8,9] The gold standard method to diagnose mucositis is a biopsy from the small intestine. As this procedure is invasive and therefore not clinically feasible, clinical scores and biomarkers are used to assess severity of mucositis.[10-13] Several mucositis scores are available although there are differences regarding the focus on oral- versus GI-mucositis. The Daily Gut Score (DGS) quantifies GI-mucositis by scoring frequency, consistency and incontinence of feces, nausea, vomiting, abdominal complaints and the ability of oral intake.[12] Nevertheless, the clinical assessment scale is subjective, based on symptoms that may not be specific for mucositis and could be influenced by analgesic agents.[14]

Both citrulline and albumin plasma concentration are also used as biomarkers for mucositis of which citrulline is the most potent.[14] Citrulline is a non-protein amino acid almost exclusively produced by enterocytes of the small intestine. As mucositis develops, mucosal barrier integrity deteriorates which is associated with a reduced citrulline plasma concentration. Consequently, citrulline serves as a biomarker for GI-mucositis. Plasma citrulline <10 µmol/L is associated with severe mucositis, 10-30 µmol/L is associated with mild mucositis, while >30 µmol/L is considered normal.[13,15,16] Citrulline plasma concentration starts declining shortly after initiation of chemotherapy. The lowest values are observed 7-10 days after start of high dose chemotherapy after which citrulline levels rise to normal values around 21 days after high dose chemotherapy.[13]

Besides mucositis, concomitant medication could also influence ciprofloxacin oral absorption. Prokinetic agents like metoclopramide or clarithromycin increase gastric motility and augment esophageal peristalsis which could accelerate oral absorption.[17] Proton-pump inhibitors and antacids could delay gastric emptying by increasing gastric

pH while opioids may delay oral absorption as a result of reduced intestinal motility.[17] Bioavailability may be reduced by co-ingestion with Al^{2+}, Ca^{2+}, Fe^{2+} or Mg^{2+}.[5]

Ciprofloxacin pharmacokinetics in patients with chemotherapy for hematological malignancies showed conflicting results in three case-series (participants n≤8 per series) as exposure was found to be unaltered or decreased.[18-20] Two studies did not report severity of mucositis at all while one study only used clinical markers to describe severity of oral mucositis. Consequently, a knowledge gap remains regarding the influence of GI-mucositis on oral absorption and clearance of ciprofloxacin, risking underexposure and possibly higher infection-related mortality.

In a cohort of neutropenic patients treated for a wide variety of hematological malignancies leading to a high risk of mucositis we investigated ciprofloxacin pharmacokinetics and evaluated if mucositis influences oral bioavailability and clearance, compared to healthy volunteers.

PATIENTS AND METHODS

Data

Data from three cohorts consisting of only hematological patients were collected in two Dutch academic hospitals. Cohort 1 was a prospective observational cohort at the Amsterdam UMC, location Academic Medical Centre (Amsterdam UMC, location AMC). Patients were recruited between March 2019 and December 2020 n=41 (NTR7520). Cohort 2 consisted of participants in a dense sampling study into micafungin pharmacokinetics (NCT02172768) who simultaneously received ciprofloxacin prophylaxis.[21] Cohort 3 consisted of participants in a dense sampling study after posaconazole pharmacokinetics (NCT02805946) who received ciprofloxacin prophylaxis.[8] Patients with concomitant use of ciprofloxacin on pharmacokinetic (PK)-sampling days of micafungin or posaconazole (n=2 and 4 patients, respectively) were selected. Finally, to compare the impact of mucositis caused by high dose chemotherapy on oral absorption, these data were compared to data from a previously performed dense-sampling pharmacokinetic study (n=28 with 391 samples) after oral and intravenous ciprofloxacin administration in healthy volunteers and obese patients (NTR6058).[22]

Hematological patients receiving reduced intensity conditioning regimens for allogeneic HSCT, first remission-induction chemotherapy for AML/myelodysplastic syndrome or CAR-T cell infusion for lymphoma and who received orally administered ciprofloxacin tablets (500 mg twice daily) for gram-negative prophylaxis were eligible for inclusion if they were legally competent and at least 18 years of age. Exclusion

criteria were admission to the intensive care unit, receiving renal replacement therapy or patients unable to take oral medication due to progression or worsening of mucositis and patients with a previous ciprofloxacin treatment course for whom discontinuation lasted less than 48 hours.

In cohort 1, two samples were collected around 1-2 hours after oral administration, one prior to administration and one random sample, all within 72 hours around 7 days after initiation of chemotherapy. Additionally, left-over material from routine sampling at >7 days after initiation of chemotherapy was collected. Blood samples were centrifuged immediately and plasma was stored at -80ºC at the clinical laboratory of the pharmacy department of the Amsterdam UMC, location AMC. In cohort 2 and 3 one trough concentration was collected daily with additional dense sampling (t= 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24) on two PK-days between day 1 and 15 after initiation of chemotherapy. Details on the sampling scheme and the schedule of the PK-days in relation to the start of chemotherapy are presented in table S1 and S2. Samples from cohort 2 and 3 were stored at -80ºC at the clinical laboratory of the department of pharmacy at the Radboud university medical center, Nijmegen, until analysis.

Data on patient characteristics (sex, age, weight, height, BMI, diagnosis, current and previous treatment details, comorbidity), ciprofloxacin treatment (dose, date and time of administration), factors leading to reduced ciprofloxacin exposure (vomiting within 2 hours after administration, interacting co-medication (ranitidine, Al^{2+}, Ca^{2+}, Fe^{2+} or Mg^{2+} containing drugs administered within 4 hours before or 2 hours after ciprofloxacin) and co-medication influencing the oral absorption process (prokinetic agents, Proton Pump Inhibitors, opioids); serum creatinine, mucositis biomarkers (albumin, citrulline) and DGS were recorded over time. To estimate glomerular filtration rate (eGFR), both indexed and de-indexed Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) and Modification of Diet in Renal Diseases (MDRD) were calculated.[23,24] De-indexing was done by multiplying the respective eGFR by 1.73/body surface area (BSA) (BSA was calculated using du Bois-du Bois formula).[25]

A single citrulline plasma sample was drawn in cohort I, simultaneously with obtaining samples collected around 1-2 hours after oral administration. In cohort 3, citrulline plasma samples were collected daily. All citrulline samples were stored on ice and centrifuged within 2 hours. Plasma was stored at -80ºC until analysis. Plasma citrulline was not determined in cohort 3 and the control group.

DGS was retrospectively scored based on data available in the electronic patient registry on every day of PK-sampling. For all six components of the DGS, patients could score 0-3 points, with 0 indicating no complaints and 3 indicating severe complaints with

that component. GI mucositis was scored as mild (1-6 points), moderate (7-12 points) or severe (>12 points).[12]

Ethics

The research protocol for cohort 1 was approved by the certified Medical Ethics Committee of the Amsterdam UMC, location AMC (NL67783.018.18). All patients provided written informed consent. Participants in cohort 2, 3 and the control group provided written informed consent before inclusion in the respective studies (clinicaltrial.gov identifiers for cohort 2 and 3: NCT02172768, NCT02805946. Dutch trial registry number for the control group: NTR6058). The institutional review board permitted additional analysis on the previously collected samples from cohort 2 and 3 and waived informed consent. Additional clinical parameters were collected from the electronic patient registry if patients gave consent for inclusion in the Radboud UMC Biobank Hematology.

The study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.[26,27]

Laboratory analysis

Total ciprofloxacin plasma concentrations were analyzed using a validated LC-MS/MS assay at the Amsterdam UMC. The validated range of the analysis is 0.020 – 5.0 mg/L.[28] Citrulline samples were analyzed using a validated UPLC MS/MS assay at the Clinical chemistry laboratory of Canisius Wilhelmina Hospital, Nijmegen.[29]

Population pharmacokinetic analysis

Concentration-time data from hematological patients and healthy volunteers were analyzed simultaneously by non-linear mixed-effects modelling using FOCE with interaction and the ADVAN6 subroutine (NONMEM; v7.4.0 with PsN; v4.7.1 and Pirana v2.9.7).[30,31] Bioavailability (F) and clearance (Cl) are the pharmacokinetic parameters of primary interest as these drive systemic exposure (measured as AUC) after oral administration. Systemic exposure can be calculated using equation 1.

$$AUC = \frac{\mathrm{F} * \mathrm{Dose}}{\mathrm{Cl}} \quad (1)$$

A previously developed PK-model for ciprofloxacin in healthy volunteers and obese patients with a two-compartment structure and transit compartments for oral absorption was used as a starting point.[22] For the group of hematological patients (cohort 1-3), all PK-parameters were estimated relative to the control group using equation (2) with a correction factor significantly different from 1.0 indicating a difference in typical value between hematological patients and the control group for the respective parameter.

$$\theta_{haematological\ patient} = \theta_{healthy\ volunteer} * \ \theta_{correction\ factor} \quad (2)$$

The influence of covariates (age, sex, weight, BMI, CKD-EPI, MDRD, citrulline, albumin, DGS, days after chemotherapy) was tested for associations with model parameters. If multiple observations were available for one individual (creatinine, citrulline, albumin, DGS and days after chemotherapy) covariates were assessed as a time varying covariate with backward interpolation.

Continuous covariates were implemented in the model using exponential or linear relationships using equation (3) and (4), respectively. Pi and Pp represent individual and population parameter estimates, X represents the exponent for a power function and Z represents the slope for the linear covariate relationship. For dichotomous covariates different parameters were estimated for the respective subgroup.

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (3)$$

$$P_i = P_p \times \left(1 + Z \times (COV - COV_{standard})\right) \quad (4)$$

In the model building process, a change in objective function value, goodness-of-fit, conditional weighted residual plots, reduction in interindividual variability and individual fit plots were used to compare models. A p-value of <0.05, representing a decrease of 3.84 in objective function value with one degree of freedom was considered statistically significant for structural parameters. In the covariate analysis a p-value of p<0.05 (objective function value decrease >3.84) was considered statistically significant in the forward inclusion step while p<0.001 (objective function value increase >10.8) was considered statistically significant in the backward elimination. Internal model evaluation and validation was done using GOF-plots, CWRES-plots split for cohort and time dependent covariates, visual predictive check (VPC) and sampling importance resampling (SIR).

Continuous data are presented as mean ± standard deviation (SD) and analyzed by t-test when normally distributed or as median ± IQR and analyzed by Mann-Whitney-U-test when not normally distributed.

After development and internal validation of the pharmacokinetic model, simulations were performed with 2500 virtual individuals per cohort with interindividual variability. The ciprofloxacin exposure, measured as AUC in hematological patients was compared to healthy volunteers after the standard of care dosing regimen of twice daily oral administration of 500mg.

RESULTS

Subject characteristics

Data of forty-seven patients (19 men and 28 women) with a wide variety of hematological malignancies were included in which 250 ciprofloxacin plasma samples were available. The oral absorption phase was captured in detail with 82 plasma samples (33%) collected in the first two hours after oral administration. Data of 28 healthy volunteers (14 men and 14 women) were included. 8 patients received semi-simultaneous oral and intravenous administration and 20 individuals received either oral or intravenous administration. In total 391 samples were collected in the control group, 178 after intravenous administration and 213 after oral administration. A detailed description of PK-data is provided in Table S2.

The majority of patients showed biochemically mild mucositis with the lowest observed citrulline (nadir) between 10-30 µmol/L (n=32, 68%) and a DGS indicating clinically mild mucositis (n=46, 98%). Clinically moderate mucositis (by DGS) was observed in 1 patient (2%) while biochemically severe mucositis (citrulline nadir ≤10 µmol/L) was observed in 9 patients (19%). Of these 9 patients, the DGS indicated clinically mild mucositis in 8 patients and moderate mucositis in 1 patient. Samples were collected median (IQR) 6 (3-11) days after start of high dose chemotherapy. In patients with multiple citrulline observations a declining plasma citrulline was observed until 10 days after start of conditioning. Concomitant medication that could influence the oral absorption process was used by 29 hematological patients (62%) at the time of PK-sampling. Drugs delaying oral absorption were used by 26 patients (89%) while drugs accelerating oral absorption were used by 14 patients (48%). Details of patient characteristics including the use of concomitant medication potentially influencing oral absorption of ciprofloxacin are presented in Table 1.

Pharmacokinetic analysis

The concentration-time profiles were best described by a two-compartment model with first order elimination and a transit compartment model for oral absorption with a correction factor of 2.07 (95%CI 1.4 – 2.5) on mean transit time for hematological patients, interindividual variability on clearance, volume of distribution and mean transit time and a proportional error model (for model structure, see Figure S1). Bioavailability and clearance were 60% and 33.2 L/h, respectively and were not significantly different between hematological patients and the control group. The degree of mucositis measured by DGS, citrulline and albumin plasma concentration as well as days after chemotherapy were investigated as potential drivers of the observed difference in the mean transit time between both groups, but evaluation of these parameters did not provide a better prediction of the observed data. Goodness-of-fit-plots show the model adequately describes the observed data and conditional weighted residual plots

Table 1: Population characteristics

	Hematological patients (n=47)	Control group (n=28)
Age	53 (47 – 64)	40 (27-52)
Sex, male (n (%))	19 (40)	14 (50)
Weight (kg)	78 (69 – 90)	123 (84-149)
Citrulline nadir (µmol/L)[a]	16 (12-23)	n.d.
Citrulline nadir ≤10 µmol/L (n)	9	n.d.
Citrulline nadir 10-30 µmol/L (n)	32	n.d.
Citrulline nadir ≥30 µmol/L (n)	4	n.d.
Albumin nadir (g/L)	42 (26 – 50)	n.d.
Daily Gut Score	1 (1-1)	n.d.
Diagnosis		n.a.
Acute leukemia	17	
Lymphoma	13	
Multipel myeloma	9	
Chronic leukemia	3	
Other	5	
Treatment (n)		n.a.
Remission-induction	19	
Autologous SCT	16	
Allogeneic HSCT	10	
Other	2	
Relevant co-medication		
Reduced bioavailability		
Magnesium hydroxide	1	0
Delayed absorption		
Proton pump inhibitor	24	0
Esomeprazole	19	
Pantoprazole	3	
Omeprazole	2	
Opioid	7	0
Oxycodone	5	
Morphine	1	
Fentanyl	1	
Tramadol	1	
Accelerated absorption		
Metoclopramide	13	0
Metoprolol	1	0
Clarithromycin	1	0
Serum creatinine (µmol/L)	74 (62 – 89)	72 (64 – 80)
CKD-EPI (ml/min/1,73 m^2)	97 (80 – 112)	134 (118 – 149)
$CKD\text{-}EPI_{de\text{-}indexed}$[b] (ml/min)	84 (68 – 105)	102 (95 – 109)
MDRD (ml/min/1,73 m^2)	96 (78 – 121)	126 (110 – 154)
$MDRD_{de\text{-}indexed}$[b] (ml/min)	82 (66 – 115)	98 (90 – 108)

Data are presented as median (IQR) unless stated otherwise. For citrulline and albumin the lowest observed value is reported if multiple observations were available per patient. For serum creatinine and corresponding estimators of GFR the observation at baseline is reported. Daily Gut Score (DGS) 1 represents mild mucositis (1-6 points on the DGS) and 2 represents moderate mucositis (7-12 points on the DGS). HSCT: Hematopoietic stem cell transplant, N.a.: Not applicable, nadir: lowest observed value for an individual, N.d.: Not determined, SCT: Stem cell transplant. [a] *Citrulline plasma concentration was determined in 45 hematological patients*
[b] *De-indexed by multiplying CKD-EPI or MDRD by BSA/1.73.*

indicate no model misspecification as residuals were randomly spread against time after start of ciprofloxacin, predicted plasma concentration, plasma albumin, plasma citrulline and days after chemotherapy (Figure S2). The use of concomitant medication in the hematological patients showed no significant association with altered ciprofloxacin pharmacokinetics in hematological patients. Also, the predictive performance of citrulline plasma concentration as a biomarker for impaired oral absorption was not significantly different for patients receiving stem cell transplant compared to patients receiving other therapy (Figure S3). Clearance, bioavailability and volume of distribution were unaffected by mucositis. Total body weight and renal function also did not provide a statistically significant improvement of the fit when tested as covariates on these parameters. Internal model validity was confirmed using VPC stratified for hematological group and control group (Figure S4). Model parameters and their uncertainty based on SIR are shown in Table 2, the mean percentage error is -5.4%.

Table 2: Pharmacokinetic parameter estimates for the final model

Parameter	Estimate (%RSE)	SIR 95% CI
CL (L/h)	33.2 (6.9)	29.9 – 37.0
V_c (L)	69.0 (19.1)	50.7 – 92.8
V_p (L)	140 (10.6)	120 – 160
Q (L/h)	71.4 (13.4)	57.3 – 83.5
F	0.603 (8.5)	0.535 – 0.669
K_a (h^{-1})	1.35 (14.5)	1.08 – 1.70
MTT Control group (h)	0.317 (13.1)	0.230 – 0.369
Relative MTT Hematological patients[a]	2.07 (14.8)	1.41 – 2.50
NN (n)	10.9 (40.2)	6.51 – 15.8
Interindividual variability (%)[b,c]		
CL	28.1 (12.8)	20.7 – 34.3
V_c	86.7 (23.7)	55.9 – 134
MTT	82.6 (13.2)	74.7 – 117
Residual error (%)[b]		
σ prop[d]	21.4 (5.9)	19.4 – 23.1

CL: Clearance from the central compartment, F: bioavailability, Ka: Absorption rate constant, MTT: Mean Transit Time, NN: Number of transit compartments, Q: Intercompartmental clearance, RSE: Relative Standard Error, SIR: sampling importance resampling based on 5000 samples and 1000 resamples, Vc: Volume of distribution of the central compartment, Vp: Volume of distribution of the peripheral compartment

*a absolute MTT for hematological patients is 0.656 h (according to Eq. 1: 0.317 h * 2.07 = 0.656 h)*

b Calculated by $\sqrt{(e^{\omega^2} - 1)}$

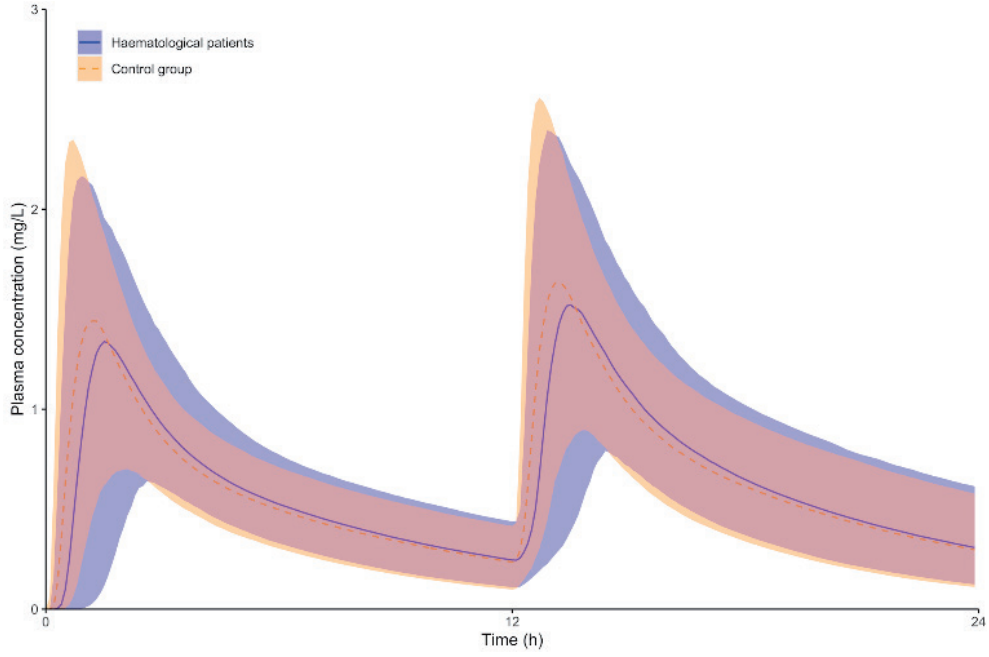
c η-shrinkage: CL 5%, V_c 26%, MTT 26%,

d ε-shrinkage: 11%

Model-based dose evaluations

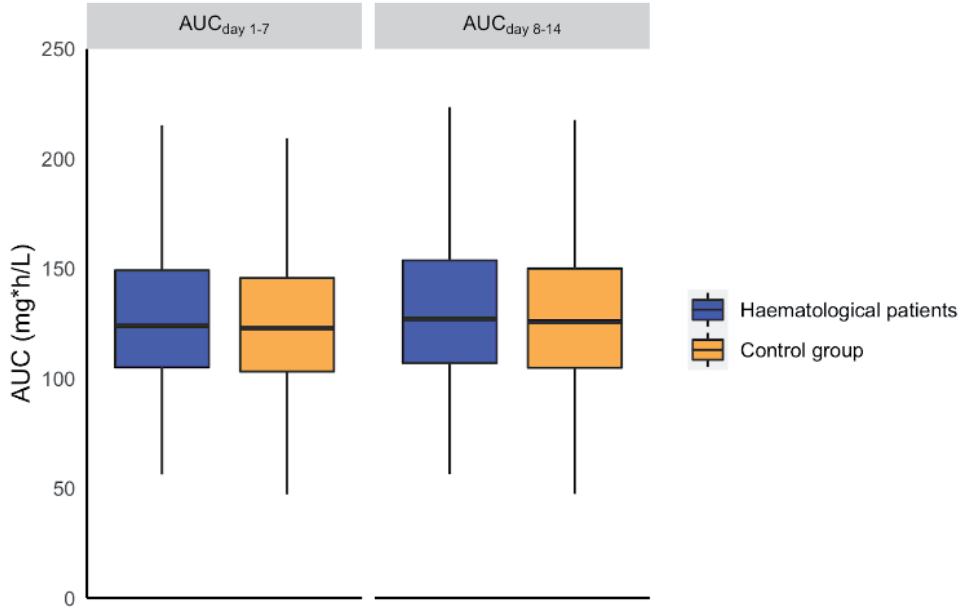
Using the final and internally validated model, exposure that can be expected upon the standard of care dosing regimen of a twice daily oral ciprofloxacin administration of 500 mg was evaluated. The median (IQR) time to ciprofloxacin C_{max} is 1.5 (1.2-2.1) hours for hematological patients and 1.2 (1.0-1.5) hours for the control group as shown in Figure 1. In the first week of treatment median (IQR) cumulative $AUC_{day\ 1\text{-}7}$ is 124 (105 – 149) mg*h/L for hematological patients and 123 (103 – 146) mg*h/L for healthy volunteers. In the second week of treatment median (IQR) cumulative $AUC_{day\ 8\text{-}14}$ is 127 (107 – 154) mg*h/L for hematological patients and 126 (105 – 151) mg*h/L for healthy volunteers as displayed in Figure 2.

Figure 1



Concentration-time curve (median (line) and 95% prediction interval (shaded area)) for hematological patients (pink) and healthy volunteers (teal) after twice daily oral ciprofloxacin 500mg. Data based on simulations with n=2500 per subgroup. The median simulated time to ciprofloxacin C_{max} is 1.5 hours for hematological patients and 1.2 hours for the control group

Figure 2



Boxplots illustrating similar cumulative systemic exposure in the first- and second week of therapy ($AUC_{day\ 1-7}$ left panel, $AUC_{day\ 8-14}$ right panel) for hematological patients (blue) and the control group (orange). Data are based on Monte Carlo simulations (n=2500 per subgroup) after the standard of care dosing regimen of 500mg PO twice daily.

DISCUSSION

Ciprofloxacin pharmacokinetics in patients with hematological malignancies and mild mucositis capable of oral intake and healthy volunteers is comparable. Oral absorption remains adequate during the whole chemotherapy treatment course, even in the second week after high-dose chemotherapy when mucositis is most severe. However, oral absorption was slower in hematological patients. Therefore, hematological patients with mild to moderate mucositis capable of oral intake can receive orally administered ciprofloxacin as gram negative infection prophylaxis.

We included 47 patients with a wide variety of hematological malignancies and a broad range in severity of underlying disease at different time points in their treatment course. The majority of participants capable of oral ciprofloxacin intake had clinically mild mucositis based on the DGS and as a result few data on oral absorption and clearance of ciprofloxacin could be collected in patients with clinically moderate mucositis and no

data was collected in patients with clinically severe mucositis. Patients unable to take oral medication due to progression or worsening of mucositis or developing fever were switched to intravenous therapy by their treating physician. There are no strict criteria for when to switch from oral to intravenous therapy. Yet, our results indicate that the clinical decision of the treating physician to switch patients from oral to intravenous therapy is at least not too late as no underexposure was observed. The majority of hematological patients used concomitant medication that could accelerate or delay the oral absorption process. Although the use of concomitant medication delaying oral absorption may have contributed to the observed increased time to C_{max} in hematological patients compared to healthy volunteers, the use of delaying concomitant medication was not a statistically significant covariate. Most importantly, only 1 patient used concomitant medication that could decrease bioavailability. Therefore, it is unlikely that the absence of a correlation of mucositis with ciprofloxacin exposure is attributable to the use of concomitant medication.

In our study the degree of mucositis was objectified using the most adequate and feasible clinical scores and biomarkers. Hematological patients suffered from mild mucositis in the opinion of the treating physician and were capable of oral ciprofloxacin intake. DGS corresponded with mild to moderate mucositis while citrulline plasma concentration ranged from values corresponding with normal values to severe mucositis. A mucositis scoring mismatch was observed in nine patients (19%) as citrulline plasma concentration showed severe mucositis (nadir <10 µmol/L) while DGS suggested mild (n=8) or moderate (n=1) mucositis. Four of these patients did not switch to intravenous therapy at any time during their treatment course, indicating no development of clinically severe mucositis in the opinion of the attending physician. Nevertheless, uncertainty remains if patients with mild mucositis according to the DGS actually showed mild mucositis in the small intestine. As patients were capable of oral intake and the physician judged mucositis to be generally mild we chose to draw conclusions regarding mild to moderate mucositis despite citrulline plasma concentrations corresponding with severe mucositis. Observations in patients treated with intravenous antibiotics whom were subsequently switched back to oral ciprofloxacin after clinical improvement were adequately described by our model. This may suggest ciprofloxacin oral absorption is not significantly altered in patients with a temporarily worsening clinical condition. The DGS was retrospectively scored based on data available in the electronic patient registry. Possibly, some components of the DGS may have been incompletely registered which could have led to an underestimation of mucositis severity using the DGS which is a limitation to our study. Also, citrulline was measured only once for participants in cohort 1. Although citrulline was observed when mucositis is expected to be worst mucosal damage may have worsened after, or was already improving at the time of monitoring. Therefore, the citrulline nadir may have been lower than the observed

value. An important strength of our study is the comparison of ciprofloxacin PK data in hematological patients with data from 28 healthy individuals as a PK reference standard, to compensate for the lack of a formal PK/PD target for gram negative prophylaxis using ciprofloxacin.

Three previous case-series reported contradictory results on exposure of orally administered ciprofloxacin in patients with hematological malignancies.[18-20] Two studies found no difference in drug concentration between hematological patients with mucositis and data from literature, although another study found a reduced drug concentration in patients with hematological malignancies.[18-20] Since these reports observed only 8, 6 and 5 patients, the external validity of the respective case-series is limited.[18-20] Moreover, two of the three case-series did not report severity of mucositis at all while one study focused on severity of oral mucositis and in contrast to our study the role of biomarkers was not evaluated before. In order to capture the severity of mucositis at the site of absorption GI-mucositis scores and biomarkers were analyzed concomitantly.

Ciprofloxacin is subject to OATP1 and OAT3 carrier mediated absorption.[32] Disruption of the mucosa could negatively impact OATP1 and OAT3 carrier capacity but at the same time mucosal barrier function may be impaired. As a result, both an increased and decreased rate of absorption and bioavailability could be anticipated. Hematological patients showed an increased time to C_{max} although this was not associated with a significant alteration in bioavailability. Both active and passive processes play a role in ciprofloxacin absorption. Therefore, the slightly longer time to C_{max} in hematological patients could theoretically be caused by a negative impact on active absorption as a result of mucositis while the net-influence on bioavailability remains negligible.

In patients with severe mucositis treated with IV ciprofloxacin, further research may be needed to clarify if destruction of the mucosa impacts the trans-epithelial intestinal secretion route of ciprofloxacin as ciprofloxacin clearance could still be altered.

In conclusion, we found no significant influence of mild mucositis on ciprofloxacin bioavailability or clearance. This study supports oral dosing of ciprofloxacin 500 mg twice daily as gram negative infection prophylaxis in hematological patients with mild to moderate mucositis capable of oral intake.

Acknowledgements, funding and disclosures

The authors thank the patients who were willing to take part in this study, the nursing staff of the hematology departments for their help, Marcel Pistorius and his colleagues from the Laboratory of Clinical Pharmacology for ciprofloxacin concentration measurement, the staff of the clinical laboratory for identifying waste material of previously collected blood samples.

This research was funded by a research grant from Tergooi MC, Hilversum.

R.J.M Brüggemann declares no interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead sciences, Merck Sharpe and Dohme Corp., Mundipharma Inc. and Pfizer Inc. All payments were invoiced by the Radboud University Medical Center. P.D. van der Linden declares membership of the compliance committee of STIZON and is treasurer of the Dutch Working party on Antibiotic Policy (SWAB), K.P. van Rhee, S.L. de Vroom, R.M. van Hest, S.H. Tonino, E. Molendijk, N.M.A. Blijlevens, R.A.A. Mathôt, C.A.J. Knibbe and S.E. Geerlings declare no conflict of interest.

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Supplementary material

Table S1: Study procedures and handling of samples

	Cohort I	Cohort II	Cohort III	Control group
Study acronym		MATADOR	PIRANA	AMIGO
Site	Amsterdam University Medical Center, Amsterdam	Radboud University Medical Center, Nijmegen	Radboud University Medical Center, Nijmegen	Radboud university Medical Center and St Antonius hospital
Design	Prospective observational cohort	Randomized open-label multiple-dose intervention study (micafungin)	Randomized open-label, multiple-dose, multiple-dose level intervention study (posaconazole)	Open-label prospective pharmacokinetic intervention study (ciprofloxacin)
Sampling scheme	2 peak samples, 1 trough sample, 1 random sample. All collected within 72 hours >7 days after conditioning. Additional scavenged sampling from left-over material from routine monitoring	Daily trough sample at 8:00 AM. Rich sampling on day 4 or 5 and day 8 at: t= 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 after micafungin administration.	Daily trough sample at 8:00 AM. Rich sampling on day 7, 12 and 16 at: t= 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 after posaconazole administration.	Dense sampling until 12 hours after administration with 11 samples after IV administration, 15 samples after PO administration and 17 samples after semi-simultaneous administration.
Handling of samples	Ciprofloxacin: centrifuged the same day Citrulline: stored on ice and centrifuged within 2 hours after collection	Ciprofloxacin: centrifuged the same day Citrulline: not studied	Ciprofloxacin: Centrifuged the same day Citrulline: stored on ice and centrifuged within 2 hours after collection	Ciprofloxacin: Centrifuged the same day
Storage of samples	-80°C until analysis	-80°C until analysis	-80°C until analysis	-80°C until analysis
Albumin monitoring	Routine care, 8:00 AM	Routine care, 8:00 AM	Routine care, 8:00 AM	Not studied
Citrulline monitoring	Obtained once, simultaneously with the first peak sample	Not studied	Daily at 8:00 AM	Not studied
DGS monitoring	Every PK day. Retrospectively collected from EHR	Every PK day. Retrospectively collected from EHR	Every PK day. Retrospectively collected from EHR	Not studied

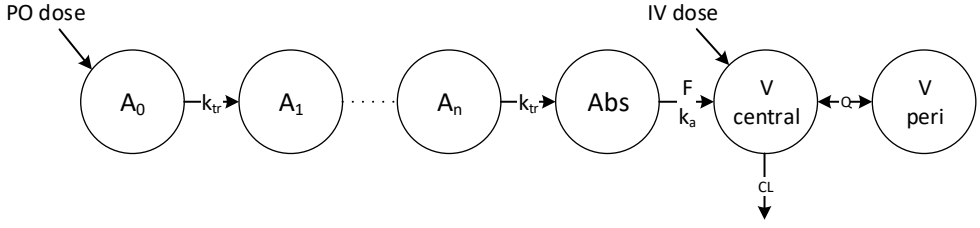
DGS: Daily Gut Score, EHR: Electronic Health Registry

Table S2: Description of pharmacokinetic data

	Cohort I	Cohort II	Cohort III	Control group	All hematological patients (Cohort 1,2,3)
Study acronym		MATADOR	PIRANA	AMIGO	
Patients (n)	41	2	4	28	47
Ciprofloxacin route of administration	PO	PO	PO	PO and IV	
Samples (n)	157	51	42	Total: 391 PO: 213 IV :178	250
Samples per patient (n)	3.8	25.5	10.3	PO: 7.6, IV: 6.4	5.3
Peak samples (n (%)) (0-2h after administration)	58 (37%)	15 (29%)	9 (21%)	PO: 92 (43%) IV: 45 (25%)	82 (33%)
Midway samples (n (%)) (2-10 h after administration)	41 (26%)	21 (41%)	10 (24%)	PO: 111 (52%) IV: 116 (65%)	72 (29%)
Trough samples (n (%)) (10-14h after administration)	54 (34%)	8 (16%)	10 (24%)	PO: 10 (5%) IV: 17 (10%)	72 (29%)
Wash-out samples (n (%)) (14-28h after administration)	4 (3%)	7 14%)	13 (31%)	PO: 0 (0%) IV: 0 (0%)	24 (10%)
Sampling at days after start of conditioning (median – IQR)	6 (3-12)	11 (7-15)	4 (1-7)	Not studied	6 (3-11)
Citrulline samples (n)	41	Not studied	24	Not studied	65
Albumin samples (n)	82	20	9	Not studied	111

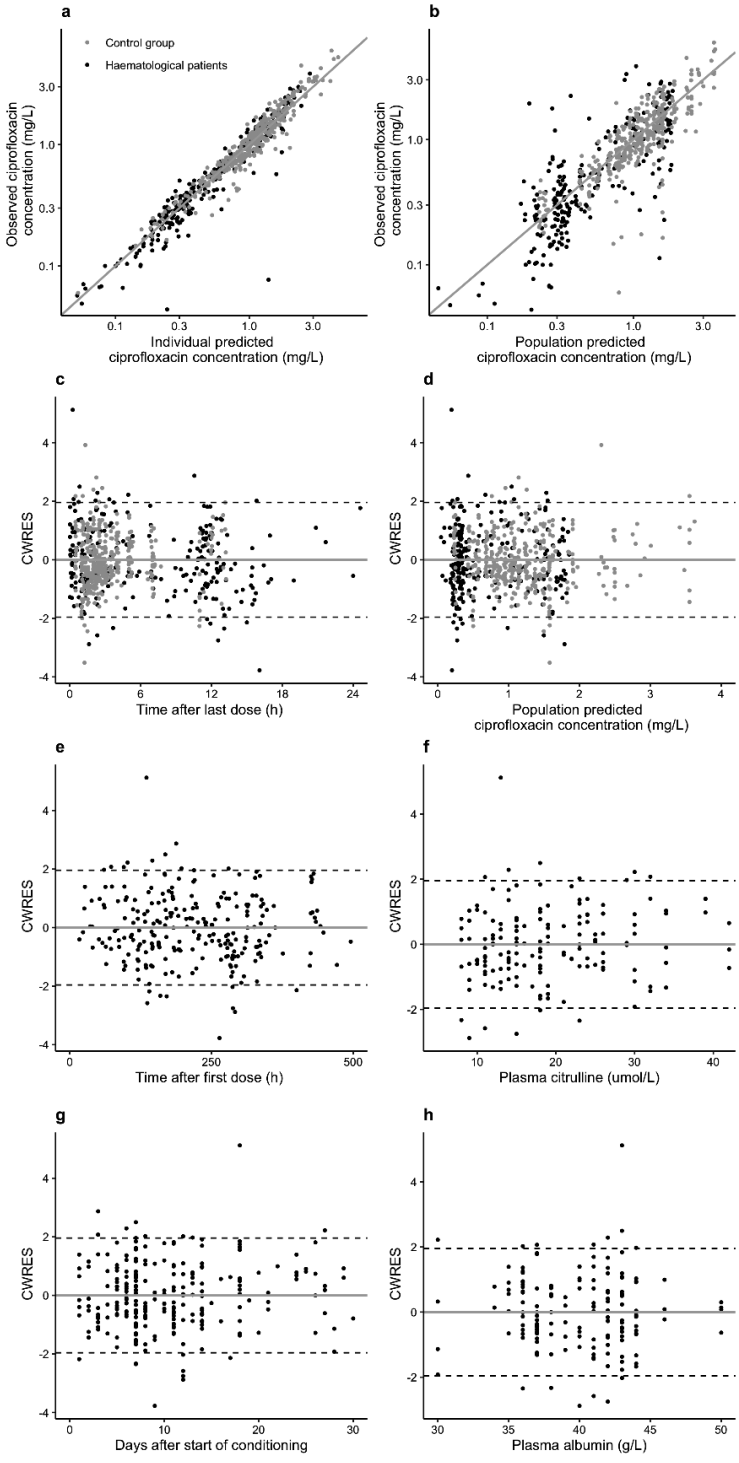
IQR: Inter-quartile range, IV: intravenous administration, PO: oral administration

Figure S1: Structure of the pharmacokinetic model



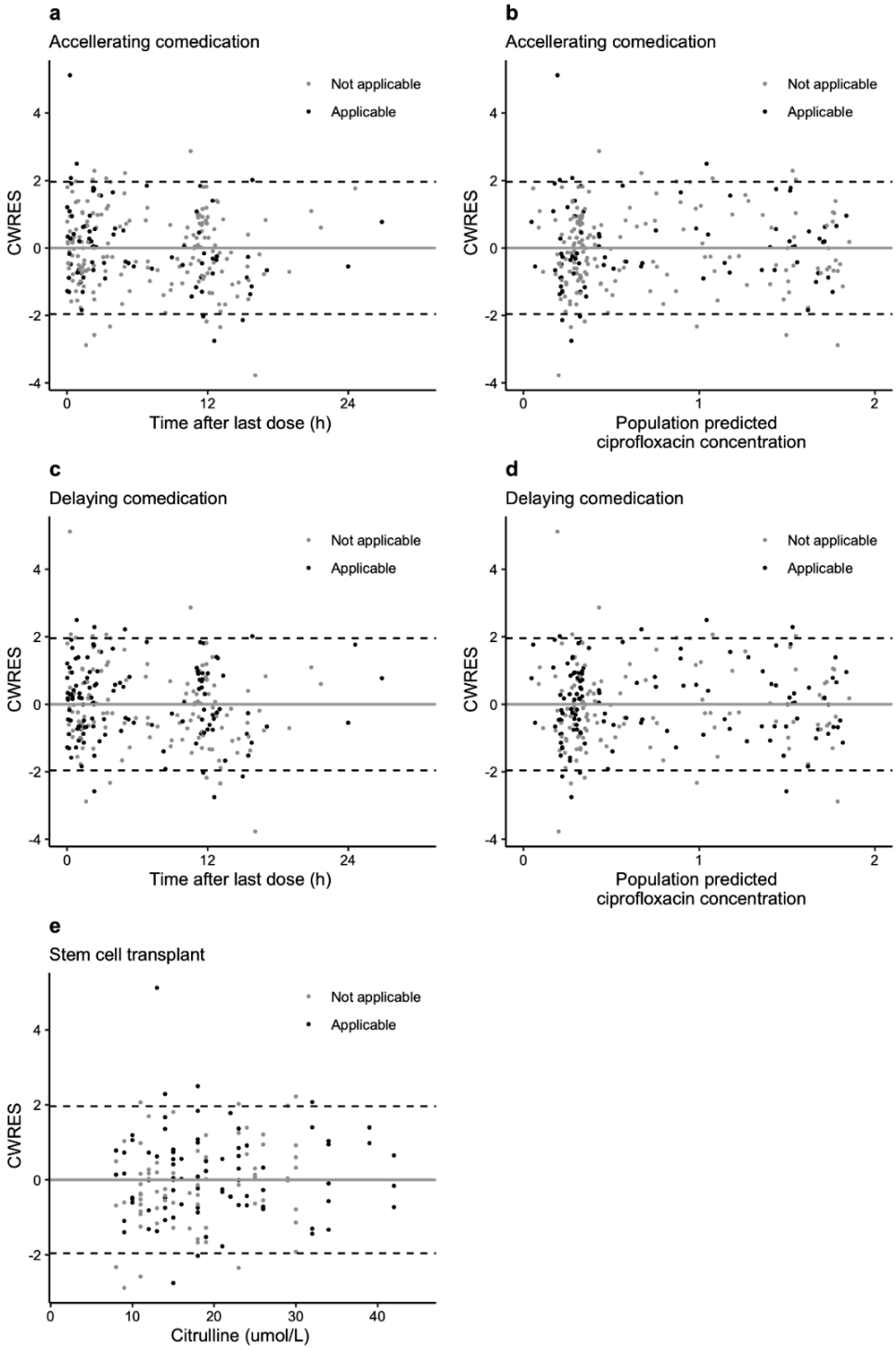
Abs: Absorption compartment, A_n: Transit compartment (n), CL: Clearance from the central compartment, F: Bioavailability, k_a: absorption rate constant, k_{tr}: transit rate constant, Q: Intercompartmental clearance, $V_{central}$: Central volume of distribution, V_{peri}: Peripheral volume of distribution.

Figure S2: Diagnostic plots of the final pharmacokinetic model



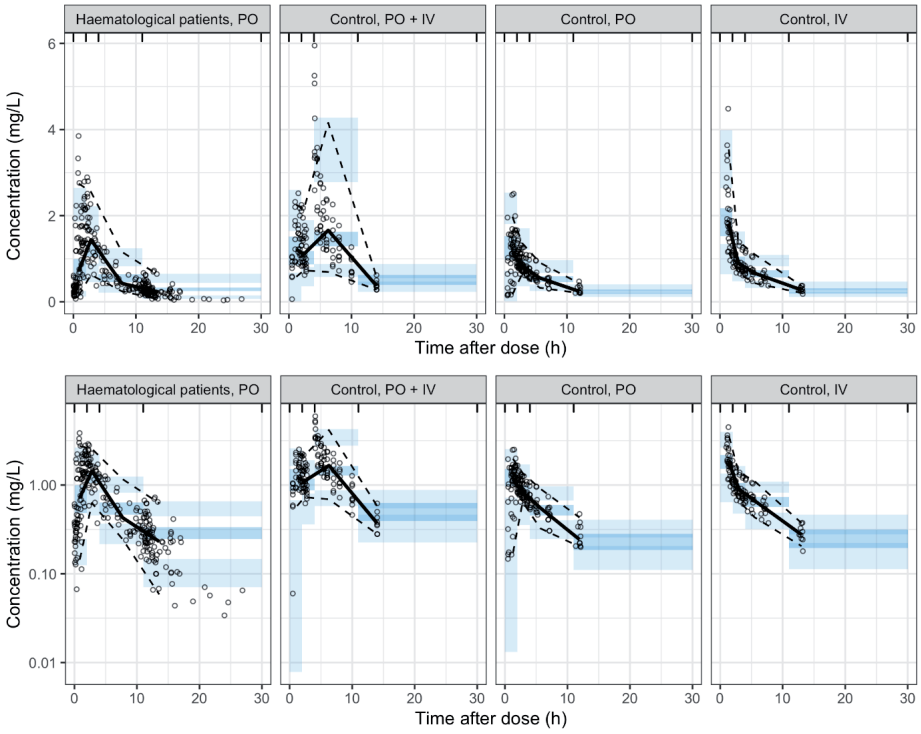
Diagnostic plots of the final model for hematological patients (black dots) and the control group (grey dots).
a: Individual predicted plasma concentrations versus observed plasma concentrations,
b: Population predicted plasma concentrations versus observed plasma concentrations.
c: CWRES versus time after last dose,
d: CWRES versus Population prediction
e: CWRES versus time after first dose,
f: CWRES versus Plasma citrulline,
g: CWRES versus days after start of conditioning,
h: CWRES versus plasma albumin.
The grey line indicates the line of identity and the dashed lines indicate the range within 95% of the observations are expected to fall. For plots e, f, g and h only hematological patient data is presented.

Figure S3: Diagnostic plots for concomitant medication use and stem cell transplant



Conditional weighted residuals (CWRES) plots of the final model for potential covariates in hematological patients showing trends versus time (a, c, e), predicted plasma concentration (b, d, f) or citrulline plasma concentration (g). Black dots represent observations where the potential covariate is applicable, grey dots represent observation where the potential covariate is not applicable.
a: Use of comedication potentially accelerating oral absorption, residuals versus time after dose,
b: Use of comedication potentially accelerating oral absorption, residuals versus PRED,
c: Use of comedication potentially delaying oral absorption, CWRES versus time after dose,
d: Use of comedication potentially delaying oral absorption, CWRES versus PRED,
e: CWRES versus citrulline plasma concentration for patients receiving stem cell transplant.
The grey line indicates the line of identity and the dashed lines indicate the range within 95% of the observations are expected to fall.

Figure S4: Visual Predictive Check of the final model



Visual predictive check of the final model stratified by subgroup (Hematological patients n=47, control PO+IV n=8, Control PO n=10, Control IV n=10) on linear scale at the top and on logarithmic scale at the bottom. The observed data are shown as circles with the median and 2.5th and 97.5th percentile of the observed data shown as a solid black line and the upper and lower dashed lines, respectively. The blue areas represent the 95% confidence interval of the simulated median (dark blue) and 5th and 95th percentile (light blue) of the simulated concentrations based on 1000 simulations of the original dataset. Vertical lines at the top of the panels represent the bins.
PO represents 500mg oral ciprofloxacin administration, PO+IV represents semi-simultaneous 500mg oral administration followed by 400mg IV infusion 3 hours after the oral administration, IV represents 400mg ciprofloxacin IV infusion.

Part IV

Summary of main findings, considerations and perspectives

CHAPTER 7

7

Unraveling the drivers of antimicrobial pharmacokinetic variability; summary of main findings, considerations and perspectives



The fluoroquinolone ciprofloxacin and the triazole fluconazole are frequently employed antimicrobial agents for infections caused by *Enterobacterales* or *Legionella* and *Candida* species, *Cryptococcus neoformans* or *Cryptococcus gattii*, respectively. Both drugs are predominantly renally cleared thus dosing regimens are often routinely adjusted, particularly in patients with severely impaired renal function[1–3]. It is well known that various pathophysiological conditions like obesity, critical illness or mucosal barrier injury can also influence the pharmacokinetics of drugs[4–6]. Nevertheless, guidance for clinicians on how therapy should be optimized in this setting is lacking for many therapeutic classes after market authorization is gained as these conditions are not typically studied during drug development. Especially individuals with obesity should be recognized as a special patient population given the current global obesity prevalence of 13% and the unpredictable influence obesity may have on the pharmacokinetics of drugs[7]. Within the domain of infectious diseases exposure in plasma or at the site of infection shows strong correlation with clinical- or microbiological cure especially when the sensitivity of the causative pathogen towards the employed antimicrobial agent is taken into account[8]. Therefore dose recommendations can be made based on previously demonstrated exposure – response relations when the changes in pharmacokinetics which may result from specific pathophysiological conditions are accounted for. By using this approach, both safe and efficacious antimicrobial therapy are assured. The work presented in this thesis studies how obesity, mucosal barrier injury, renal function and ICU admission drive pharmacokinetic variability of ciprofloxacin and fluconazole.

In Chapter 2, the first study in individuals with obesity undergoing bariatric surgery, we characterized fluconazole pharmacokinetics in order to assess the impact of obesity on fluconazole pharmacokinetics given orally or IV in order to guide dose adjustments for the obese population. We performed a prospective pharmacokinetic study with intensive sampling in obese subjects undergoing bariatric surgery (n=17, BMI≥35 kg/m^2) and non-obese healthy controls (n=8, ≤BMI 30 kg/m^2). Participants received a semi-simultaneous oral dose of 400 mg fluconazole capsules, followed after 2 h by 400 mg IV. An estimated bioavailability of 87.5% was found for both obese and non-obese subjects, with a 95% distribution interval of 43.9%–98.4%. With increasing total bodyweight, both higher clearance (CL) and volume of distribution (V_d) were found. Sex also significantly impacted V_d, as it is 27% larger in male compared with female participants. In our study population obesity clearly alters the pharmacokinetics of fluconazole. This puts severely obese adults, particularly males, at risk of suboptimal exposure, for which adjusted doses are proposed.

In Chapter 3 the second study in individuals with obesity undergoing bariatric surgery, we characterized ciprofloxacin pharmacokinetics. Our aim was to evaluate the influence of (morbid) obesity on ciprofloxacin pharmacokinetics after both oral and intravenous

administration, to ultimately guide dosing in this population. (Morbidly) obese individuals undergoing bariatric surgery received ciprofloxacin either orally (500 mg; n = 10) or intravenously (400 mg; n = 10), while non-obese participants received semi-simultaneous oral dosing of 500 mg followed by intravenous dosing of 400 mg 3 h later (n = 8).

No significant influence of body weight on bioavailability, clearance or volume of distribution was identified over the weight range of 57 – 212kg. Taking into consideration literature showing reduced soft tissue penetration in obese individuals, soft tissue concentrations were predicted to be lower in obese individuals despite similar plasma concentrations compared with non-obese individuals[9]. Based on plasma pharmacokinetics, we found no evidence of the influence of obesity on ciprofloxacin pharmacokinetic parameters; therefore, ciprofloxacin dosages do not need to be increased routinely in obese individuals. For the treatment of infections in tissue where impaired ciprofloxacin penetration is anticipated, higher dosages may be required.

In chapter 4 we compared the results from our own studies in otherwise healthy individuals versus obesity in chapter 2 & 3 with studies with other antimicrobial agents that were tested in a similar population of non-obese and obese individuals. Evaluation of 19 antimicrobial agents showed tremendous variability in the fold increase in clearance. Moreover, in contrast to patient with renal or hepatic impairment who are mainly at risk of overexposure, individuals with obesity can be at risk of both under- and overexposure. We both identified drugs with a weight based dosing regimen that do not show increased clearance in individuals with obesity resulting in overexposure, and drugs with a fixed dosing regimen that show increased clearance in individuals with obesity, resulting in underexposure. These results illustrate that gaining knowledge on the influence of obesity on clearance during early phases of drug development may allow for optimization of other phases of research. This can potentially increase the success rate of the drug and can provide clinicians with vital information as soon as the drug reaches the market. Antimicrobial therapy should be tailored to obesity-related (patho)physiological changes and to reach this goal, obese individuals should be studied during drug development.

The influence of body weight on ciprofloxacin pharmacokinetics was characterized in a relatively homogeneous population in chapter 3 although changes in pharmacokinetics may also result from other factors like renal impairment or critical illness in the real-world clinical setting. In chapter 5 we evaluated ciprofloxacin exposure in obese individuals admitted to the intensive care unit. To this end, individual patient data from 34 ICU patients with obesity (BMI >30kg/m2) from 4 studies evaluating ciprofloxacin pharmacokinetics in ICU patients were pooled. In this analysis the data after intravenous

administration collected in the study described in chapter 2 were also taken into account. This study showed that renal function, estimated by CKD-EPI, is a viable predictor for clearance in this population while both clearance and volume of distribution appear to be uninfluenced by body weight and admission to the ICU. Model based dose evaluations using a PK/PD target of AUC/MIC>125 showed that individuals with renal function >60ml/min/1.73m^2 may be at risk for suboptimal ciprofloxacin exposure for the treatment of pathogens with MIC 0.25mg/L.

In chapter 6 we investigate ciprofloxacin pharmacokinetics after oral administration in hospitalized patients with hematological malignancies and explore the impact of mucosal barrier injury on oral bioavailability and clearance in order to assure adequate systemic exposure for ciprofloxacin gram-negative prophylaxis during neutropenia. Adult hematological patients with mucosal barrier injury from two Dutch University Medical Centers received 500 mg twice daily oral ciprofloxacin. Ciprofloxacin plasma concentrations were collected at various timepoints after oral ciprofloxacin administration and at various days after completion of chemotherapy. Data obtained after oral and intravenous ciprofloxacin administration in 28 healthy volunteers without mucosal barrier injury served as a control group (391 samples). For hematological patients the degree of mucosal barrier injury was assessed using the Daily Gut Score (DGS), plasma citrulline and albumin. Data from 47 patients with a wide variety of hematological malignancies between 0-30 days after start of chemotherapy were available. The time to C_{max} was slower in hematological patients compared with healthy volunteers although no association with the degree of mucosal barrier injury (defined as DGS or citrulline) could be identified. This study supports oral dosing of ciprofloxacin as Gram-negative infection prophylaxis in hematological patients with mild-to-moderate mucosal barrier injury capable of oral intake.

Considerations and perspectives

In this section the results gathered in this thesis will be viewed and discussed in a broader perspective. The differences in pharmacokinetic behavior between drugs and between patient populations described in this thesis indicate that extrapolation of findings from drug A in population B cannot be readily extrapolated to drug C or population D. First I will reflect on differences between patients with multimorbidity and the obese population and discuss implications for research. Subsequently a framework for designing studies into clearance in individuals with obesity is provided based on a simulation study. The underlying principles and approach used for obesity can also be used to test the feasibility of a study into other patient characteristics for which the influence on pharmacokinetics are unknown.

Pharmacokinetics in individuals with obesity and hospitalized patients with multimorbidity

Adapted dosing regimens may be needed for patients with certain pathophysiological conditions. The need for dose adaptation can be determined by comparing concentration-time profiles from populations with and without this condition. Within this thesis the focus lies on exploring the influence of obesity and multimorbidity such as a hematological condition accompanied by mucosal barrier injury or ICU admission accompanied by obesity.

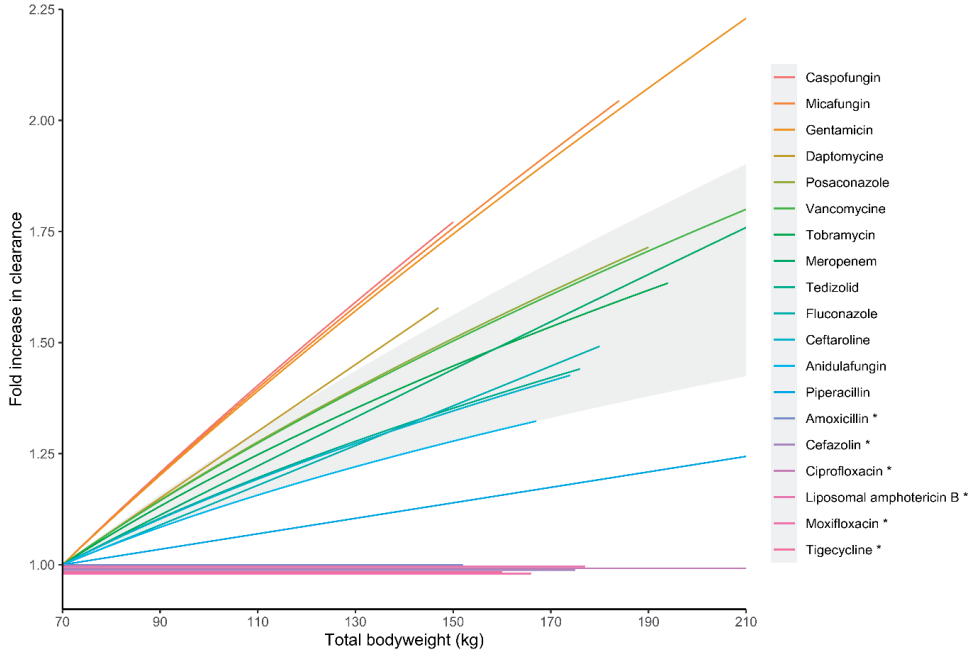
The population of hospitalized patients with multimorbidity is heterogeneous compared to the bariatric surgery population. In patients with multimorbidity as shown in this thesis, pharmacokinetic alterations may be caused by clinical interventions (e.g. fluid resuscitation or medication), disease and (co)morbidities.

To provide dosing recommendations for patients with multimorbidity the population pharmacokinetic modelling process should distinguish between the influence of disease, comorbidity and comedication on pharmacokinetics. The severity of disease and comorbidity may be quantified by taking concentrations of biomarkers (creatinine for renal function or citrulline for mucosal barrier injury (chapter 5)) or clinical scores (SOFA for ICU mortality (chapter 4) or DGS for mucosal barrier injury (chapter 5)) into account. Moreover the clinical condition of patients with multimorbidity may require treatment with drugs that could interact with the drug of interest. In some cases applying the use of interacting comedication as an exclusion criterium is infeasible. In this scenario the use of relevant comedication should be taken into account during the modelling process, as was the case in the study into the influence of mucosal barrier injury on ciprofloxacin pharmacokinetics in hematological patients (chapter 5). In this study the majority of participants used comedication that could accelerate (metoclopramide) or delay gastric emptying (proton pump inhibitors and opioids).

To determine the influence of obesity on ciprofloxacin and fluconazole pharmacokinetics, data from patients undergoing bariatric surgery were analyzed in conjunction with data from individuals without obesity (chapter 2 and 3). Studying the influence of body weight on pharmacokinetic patients that are scheduled for bariatric surgery allows study procedures to be planned ahead of time, in contrast to for instance studies in ICU patients. Bariatric surgery patients are relatively healthy, despite being obese, as they are deemed to be fit for surgery. Moreover other patient characteristics that could influence pharmacokinetic behavior (severe hepatic- or renal insufficiency and interacting comedication) can be accounted for in the inclusion criteria. Therefore potential influences on pharmacokinetics of the drug of interest are kept to a minimum in bariatric surgery patients at the time of surgery. Nevertheless anesthesia and bariatric

surgery itself could marginally influence pharmacokinetics. As the blood pressure is tightly monitored during surgery and blood loss is minimal (usually <100 mL), this influence is expected to be negligible.

Figure 1



Each line represents an antimicrobial agent visualizing the fold increase in clearance from plasma with increasing body weight compared to a 70kg individual.
**Amoxicillin, cefazolin, ciprofloxacin, liposomal amphotericin B, moxifloxacin and tigecycline show no influence of body weight on clearance and therefore overlap at Fold increase in clearance = 1.0.*
The grey shaded area represents a moderate influence of body weight on clearance with a fold increase in clearance of a 140kg individual to a 70kg individual of 1.25 – 1.5. A fold increase in clearance below the grey area represents no significant influence on clearance, a fold increase in clearance above the grey area represents a strong influence of body weight on clearance.
For cefazolin, ceftarolin, daptomycin, meropenem, piperacillin and tobramycin drivers of clearance were identified that are not strictly weight based (age, height, serum creatinine); for these drugs values of the respective drivers were fixed at the median value in order to visualize the influence of body weight on clearance. The length of the line corresponds with the maximum total body weight in the study population, with a maximum of 210kg.

Considerable heterogeneity in the influence of body weight on clearance should be anticipated for different antimicrobial agents, as described in chapter 4 and illustrated in figure 1. When new drugs currently reach the market there is still a lack of data on

the influence of obesity and multimorbidity on clearance which hampers employing the most optimal maintenance dose in special patient populations. With regard to dosing antimicrobials in individuals with obesity the aim should be to determine the optimal dosing strategy, i.e. fixed dose when clearance is uninfluenced by obesity and weight-based dosing when obesity has a significant influence on clearance. In the meantime, there is consensus that the influence of obesity on pharmacokinetics should be addressed although there is no guidance on how these studies should be shaped[10,11]. In the next chapter a simulation study is used to illustrate how a study into the influence of body weight on clearance, which preferably should take place during drug development, may be shaped.

Shaping a study design for characterization of the influence of obesity on drug clearance

Individuals with obesity are not recognized as a special patient population during drug development[10]. As a result, currently no guidance is available on how pharmacokinetics studies exploring clearance in individuals with obesity should be conducted. To illustrate how such studies could be designed, a case study using a rich sampling design for individuals with obesity similar to our studies in bariatric surgery patients is presented. The aim is to describe how the required sample size can be determined and what precision (expressed as prediction error of clearance over the weight range of 70 – 180kg) could be considered acceptable. The concepts applied in this analysis can also be used to design trials focusing on pharmacokinetic alterations in other subpopulations.

The aim of a pharmacokinetics study in individuals with obesity is to gain insight in whether and how pharmacokinetic are altered. Ultimately, these insights can be used to provide recommendations for loading- and maintenance doses in this population. For renal- and hepatic insufficiency clearance typically decreases while for obesity, and multimorbidity, clearance may be impaired, unchanged or increased. Guidelines on pharmacokinetics studies in renal impairment state that a dedicated study is warranted during drug development if the renally cleared fraction of a drug is >0.3[11]. Although there is a natural boundary for hepatic- and renal insufficiency as organ specific clearance can never be below 0 ml/min, a clear upper boundary for body weight seems to be lacking in the current era of obesity. The magnitude of the influence of obesity on clearance can be quantified by comparing the fold increase in clearance between individuals with body weight of 140kg and 70kg. This influence was found to differ between 1.0 (no influence) and 1.7 as shown in figure 1[12]. A fold increase in clearance >1.25 is considered clinically relevant. Given this heterogeneity and the unpredictable nature of this influence, a full pharmacokinetic study seems prudent for all new drugs with systemic exposure.

The following three questions determine how trials aimed at quantifying the influence of body weight on clearance may be shaped:

- What sample size is needed to detect a fold increase in clearance for an individual of 140kg compared to 70kg of 1.25 with a power of 80%?
- If the percentage error of clearance (between simulated and estimated clearance over a certain weight range) is used as a measure of precision; which limits on percentage error and body weight range are feasible?
- When sample size and precision are integrated; how do differences in the distribution of bodyweight within the study population, the interindividual variability (IIV) on clearance and the fold increase in clearance modify the estimation of clearance in individuals with obesity?

Sample size

The number of participants in a study into the influence of body weight on clearance should be sufficient to ensure precise estimation of this influence while simultaneously ensuring conclusive results[10, 11]. But when is the estimation precise enough and when is conclusiveness ensured? Subject burden should simultaneously be kept to a minimum by both recruiting the least number of subjects necessary while also keeping the burden for each individual participant to a minimum.

Although there is currently no guidance on how to perform studies into the influence of body weight on clearance, a parallel with pharmacokinetics studies in renal impairment can be drawn for which guidance is already available[11]. This guidance states that the required precision and sample size should be justified. An example is to retrospectively aim for a 95% confidence interval of 60 – 140% around a (geometric) mean estimate of a relevant pharmacokinetic parameter, in this analysis a statistical power of 80% is considered acceptable[11].

Sample size calculation requires definition of the acceptable type I and type II error rate. The type I error rate is the probability to detect altered clearance in individuals with obesity when it is not truly present, which is usually set at 5% ($\alpha = 0.05$). The type II error rate is the probability to not detect altered clearance in individuals with obesity while it is truly present, which is usually set at 20% ($\beta = 0.2$). These values are also adopted in the guidance for industry on studies in individuals with impaired renal function[11].

In population pharmacokinetic analyses the required sample size can be calculated using Monte Carlo Mapped Power (MCMP)[13]. In this case a MCMP analysis using a reduced model without an influence of body weight on clearance (the null-hypothesis) is compared to a model with an influence of body weight on clearance using the above described type I and type II error rates. In the simulation study presented here the

simulated fold increase in clearance in an individual of 140kg compared to 70kg ranged from 1.0 – 1.8. The influence of various factors (the magnitude of the fold increase in clearance, IIV on clearance and composition of the study population with regard to body weight) on the required sample size are tested.

Simulations illustrate the relevance of, and the interplay between, the body weight of the study population, the fold increase in clearance for an individual of 140kg to an individual of 70kg and the IIV on clearance. Various scenarios were tested by changing one parameter at a time according to the scenarios described in table 1a and 1b. To simulate different influences of obesity on clearance, the fold increase in clearance was varied in the equation of the typical value of clearance (TVCL, equation 1). The fold increase in clearance is defined as the ratio between the typical clearance of a 140kg and 70kg individual as described in chapter 4. For example: an exponent of 0.75 in a weight-based allometric scaling function corresponds with a fold increase in clearance of 1.68 as $^{(140kg/70kg=)2}\log(1.68) = 0.75$. It is emphasized that the true value of clearance and the exponent are imputed in the simulation study and thus known, in contrast to a study in which clearance in individuals with obesity is studied.

Equation 1: $TVCL = \theta_{CL} * (WT/70)^{\,^{2}\log(Fold\ Increase\ in\ Clearance)}$

Table 1a

Composition	Simulated body weight per subgroup and inclusion ratio
A	70 – 90kg and 140 – 160kg in a **1 : 1** ratio per weight subgroup.
B	70 – 90kg and 140 – 160kg in a **1 : 2** ratio per weight subgroup.
C	70 – 90 kg, 140 – 160kg and 180 – 200kg in a **1 : 1 : 1** ratio per weight subgroup.

Description of the differences in composition of the three tested study population. All body weights are randomly sampled from the described weight band.

To illustrate the influence of the body weight of the study population on the required sample size, three different compositions were studied. A population of non-obese participants with a body weight of 70-90kg and individuals with obesity with a body weight of 140 – 160kg (Composition **A**, consisting of two body weight groups in a 1 : 1 ratio) serves as the base scenario.

In case the Composition A does not achieve sufficient power inclusion of additional individuals with obesity may be necessary. Two extension scenarios were tested: additional inclusion of participants with a body weight of 140 – 160kg (consisting of two body weight groups in a 1 : 2 ratio, composition **B**) and additional inclusion of

participants with a body weight of 180 – 200kg (consisting of three body weight groups in a 1 : 1 : 1 ratio, composition **C**).

Table 1b: Characteristics of the dataset and pharmacokinetics model

	Base scenario	Tested scenario
Dataset composition		
Dose	1000mg administered via IV infusion over 30 minutes	n.a.
Sample design	0.53, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 24 h after start of infusion	n.a
Participant body weight	Table 1a, composition **A**	Table 1a, composition **B** and **C**
1 compartment model characteristics		
CL	4 L/h	Weight was tested as a covariate on clearance by varying the fold increase in clearance according to an exponential covariate relation: Base clearance The fold increase in clearance from literature ranges from 1.0 – 1.7. The tested fold increase in clearance ranges from 1.0 – 1.8
V	50 L	n.a.
IIV on CL	20%	10%, 30%
IIV on V	20%	n.a
Proportional error	10%	n.a.

Description of the one-compartment base model parameters and a description of the tested scenarios. In all tested scenarios one parameter was changed at a time compared to the base model, unless specified otherwise. FIC: Fold increase in clearance of a 140kg individual compared to a 70kg individual.

The reported fold increase in clearance in an individual of 140kg compared to 70kg ranges from 1.0 – 1.7 for all previously studied antimicrobial agents[12]. To determine which sample size is needed to detect an influence of body weight on clearance the cut-off value for clinical relevance, a fold increase in clearance in an individual of 140kg compared to 70kg >1.25 as described in chapter 4, is used as a reference. The IIV on clearance typically ranges from 0 – 20% but may nevertheless be around 30% for well-designed rich sampling pharmacokinetics studies[14 – 21]. These reported ranges for the fold increase in clearance in an individual of 140kg compared to 70kg and IIV on clearance serve as boundaries in the Monte Carlo Mapped Power analysis. To ensure practical feasibility, the aim is to study a maximum of 6 – 12 individuals with obesity with a control population of 6 individuals.

The number of individuals required to detect the simulated fold increase in clearance in an individual of 140kg compared to 70kg with the corresponding IIV on clearance and

80% power are presented in table 2. The cell color indicates whether this difference can be detected taking the designated maxima into account (12 participants in total for composition A, with a possible extension up to 18 participants in total for composition B and C).

Table 2

	IIV on clearance 10%	IIV on clearance 20%	IIV on clearance 30%
Composition **A**: Inclusion of individuals of 70 – 90 kg + 140 – 160kg in a 1 : 1 ratio			
Fold increase in clearance			
1.25	12	34	68
1.3	10	26	62
1.5	6	12	28
1.75	6	8	14*
Composition **B**: Inclusion of individuals of 70 – 90 kg + 140 – 160kg in a 1 : 2 ratio			
Fold increase in clearance			
1.25	15	42	96
1.3	12	33	63
1.5	9	15	27
1.75	9	9	18
Composition **C**: Inclusion of individuals of 70 – 90 kg + 140 – 160kg + 180 – 200kg in a 1 : 1 : 1 ratio			
Fold increase in clearance			
1.25	9	27	57
1.3	9	18	42
1.5	9	12	21**
1.75	9	9	12

The total number of individuals required to achieve a power of 80% for virtual drugs with a fold increase in clearance of 1.25 – 1.75 and an interindividual variability on clearance of 10 -30%. The cell color indicates whether the sample size is feasible taking the designated maxima of 12 for composition A and 18 for composition B and C into account. Green: the sample size is feasible, Orange: the sample size is infeasible although a feasible sample size reaches a power between 75 – 80%, Red: the sample size is infeasibly large.

**Observing 12 individuals in composition A for a drug with a 1.75 fold increase in CL and IIV on CL 30% yields a power of 77.7%.*

*** Inclusion of 18 individuals in composition C for a drug with a 1.5 fold increase in CL and IIV on CL 30% yields a power of 79.6%*

IIV: interindividual variability

For drugs with a fold increase in clearance of 1.25 studied in a population with composition A, inclusion of 12 individuals results in 80% power if the IIV on CL is ≤10%. For drugs with a fold increase in clearance of 1.5 sufficient power is achieved if the IIV on

CL is ≤20%. For drugs with a fold increase in clearance of 1.75 the IIV on CL can be close to 30% to still achieve sufficient power. Inclusion of 6 additional individuals with a body weight between 180 – 200kg (Composition C) provides sufficient power if the fold increase in clearance is >1.5 and IIV on CL is ≤30%.

If composition A requires an unfeasibly large study population (i.e. >12 individuals) additional inclusion of individuals with a body weight of 180 – 200kg may help to achieve a power of 80% whereas additional inclusion of individuals with a body weight of 140 – 160kg only results in a marginal increase in power. This is exemplified by a virtual drug with a fold increase in clearance of 1.3 and an IIV on CL of 20%. The sample sizes with composition A – C are 26, 33 and 18, respectively. The sample sizes required to achieve 80% power using composition A and B are infeasibly large whereas the sample size of 18 participants in composition C meets the feasibility criteria. Therefore, increasing the number of individuals (composition B) seems to add less information compared to inclusion of a wider range in body weight (composition C)

The presented simulations cover a wide range of scenarios, nevertheless additional parameters may still be of relevance: drugs may exhibit multiple compartment kinetics, non-weight related covariates may also be predictive for clearance, volume of distribution could be simultaneously influence by body weight and the fold increase in clearance and the IIV on CL could be correlated.

To test the sensitivity of the proposed design, the required sample size is calculated for the 8 of 19 (42%) antimicrobials described in chapter 4 for which a clinically relevant increase in clearance was reported in individuals with obesity. In this analysis the reported final model is compared with the null-hypothesis that there is no influence of body weight on clearance for these drugs (i.e. a copy of the final model in which the influence of weight on clearance is eliminated). The required sample size using composition A – C are presented in table 3. This analysis shows that a fold increase at the borderline of clinical relevance (e.g. fold increase in clearance 1.25 – 1.3) could remain undetected if the IIV on CL is >10%, as was the case for anidulafungin. For all other previously tested drugs, a study population of 12 – 18 participants of composition A – C detects a clinically relevant increase in clearance in individuals with obesity with a power of 80%.

The study populations with composition A and C with the designated maximum of 6 participants per stratum are used in subsequent analyses into the prediction error of clearance.

Table 3

Antimicrobial	Fold increase in clearance	IIV on CL (CV%)	Sample size Composition A	Sample size Composition B	Sample size Composition C	Ref
Anidulafungin	1.25	12.5	24	27	21*	14
Fluconazole	1.31	0	6	9	9	15
Meropenem	1.39	20.8	24	24	18	16
Tobramycin	1.40	12.0	8	9	9	17
Vancomycin	1.45	17.8	16	15	9	18
Posaconazole	1.45	0	10	12	9	19
Gentamicin	1.66	18.1	8	9	9	20
Micafungin	1.67	8.1	6	9	9	21

The sample size required to detect the reported fold increase in clearance with a power of 80% at a significance level of 5%. The cell color indicates whether the sample size is feasible taking the designated maxima of 12 for composition A and 18 for composition B and C into account. Green: the sample size is feasible, Orange: the sample size is infeasible although a feasible sample size reaches a power between 75 – 80%, Red: the sample size is infeasibly large.

CL: Clearance, CV: Coefficient of variability, IIV: interindividual variability

** Observing 18 participants with the composition of study population C yields a power of 78,4%*

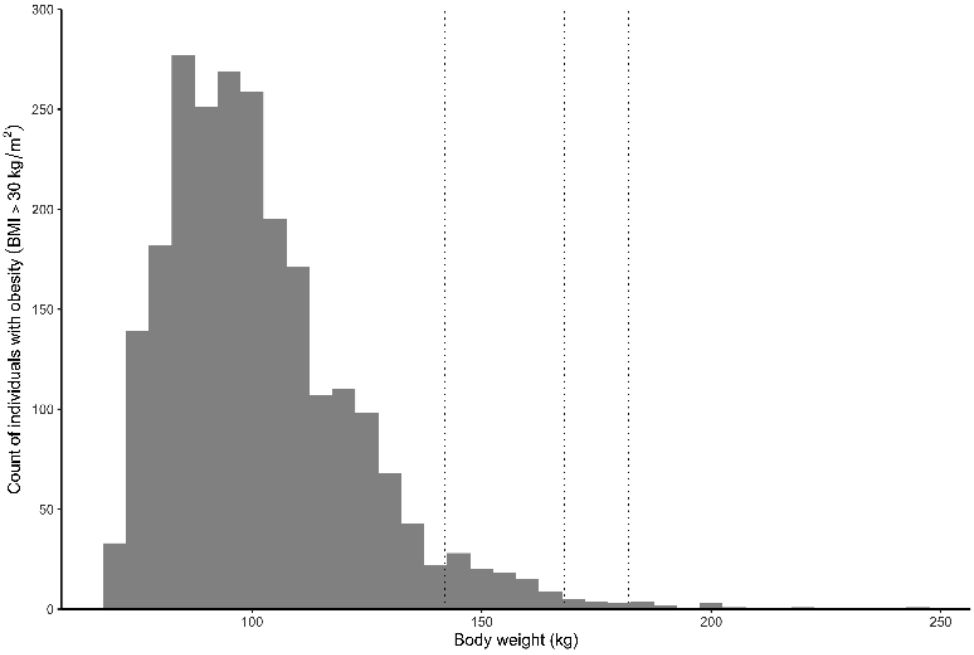
Prediction error of clearance

When studying clearance in individuals with obesity the previously described population compositions yield sufficient power. But do they also achieve sufficient precision? The precision of the estimation of clearance in individuals with obesity can be quantified by calculating the percentage error of the estimated clearance in an individual of a certain body weight. The guidance for industry on studies in renal impairment set a limit of a 95% confidence interval within 60 – 140% of a relevant pharmacokinetic parameter[11]. This value is adopted as a boundary for the analysis of precision in the estimation of clearance in individuals with obesity in the following analysis.

In renal- and hepatic impairment organ specific clearance can never be <0 ml/min which provides a natural boundary when studying the influence of these conditions on clearance. In contrast, to study the influence of body weight on clearance an upper bound in body weight needs to be defined to ensure practical feasibility. To set an upper limit, data from the National Health and Nutrition Examination Survey (NHANES) database was used to extract information on BMI from the population in the United States of America in 2017-2018[22, 23]. The histogram in figure 2 shows the distribution in body weight for all individuals in the dataset with a BMI >30kg/m^2. The median body weight is 98kg, while the 95th, 99th and 99.5th percentile correspond with body weights of 140kg, 167kg and 181kg, respectively.

The severity of obesity may worsen in the future and demographics differ between countries. Therefore, a body weight of 180kg (covering the 99.3th American body weight percentile) is used as an upper limit in our analyses in order to maximize external validity with regard to potential changes in the future composition of the population of individuals with obesity.

Figure 2



The histogram illustrates the distribution of body weight in American individuals with obesity (BMI >30kg/m^2) in 2017-2018. The dashed lines at 142kg, 167 and 181kg indicate the 95th, 99th, and 99.5th percentile of bodyweights in this population.

Simulations illustrate whether and how the estimation of clearance in individuals with obesity is influenced by the magnitude of the fold increase in clearance for an individual of 140kg compared to 70kg and the IIV on CL. To compare results for the scenarios described in table 1b, 500 virtual studies were generated using stochastic simulation and estimation which is a tool for hypothesis testing. Datasets are generated using the values described in table 1b after which the model parameters are re-estimated. In this analysis the estimations of the 500 virtual studies are compared with the simulated pharmacokinetic parameters in order to evaluate precision. An increasing PE(%) on CL is synonymous for decreased precision. The prediction error on clearance was calculated for every study (*i*) for every body weight (*j*) between 70kg and 210kg using equation 2a

– 2c. The influence of the magnitude of the fold increase in clearance and increasing IIV on CL on the percentage error are visualized by plotting the median and 95% CI prediction error versus body weight for study population A and/or C depending on the tested scenario.

Equation 2a: $Simulated\ CL = CL * (\frac{WT}{70\ kg})^{^2 log(Fold\ Increase\ in\ Clearance)}$

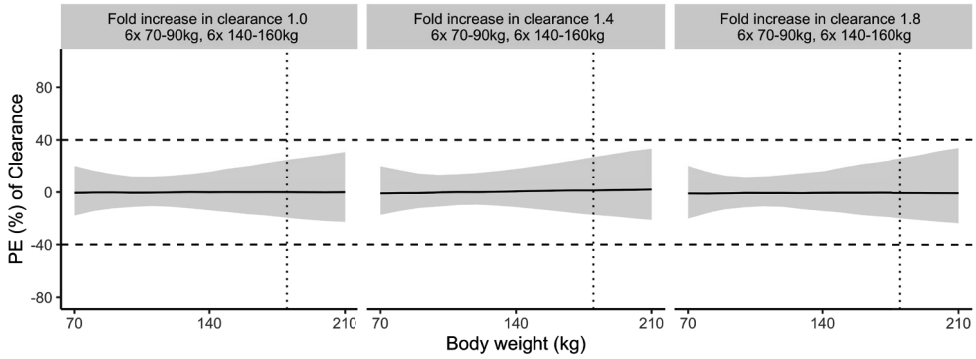
Equation 2b: $Estimated\ CL_i = \theta_{CL} * (\frac{WT}{70\ kg})^{\theta_{\exp CL}}$

Equation 2c: $Prediction\ error\ on\ CL_{i,j} = \frac{(Estimated\ CL_{TBW\ i\ kg,j} - Simulated\ CL_{TBW\ j\ kg})}{Simulated\ CL_{TBW\ j\ kg}} * 100\%$

The simulations show that the absolute value of the fold increase in clearance in an individual of 140kg compared to 70kg does not significantly influence the prediction error of clearance as the shape of the 95% CI of the PE(%) of clearance remains constant over the 70 – 180kg weight interval, as presented in figure 3. The IIV on CL does however influence the precision of the estimation of clearance as the shape of the 95% CI widens with increasing IIV on CL. A study with a sample size of 12 individuals (top row, 6 individuals with weight 70 – 90kg and 6 individuals with body weight 140 – 160kg, composition A) yields sufficient precision if IIV on clearance is ≤30%. Additional inclusion of 6 individuals with a body weight of 180 – 200kg (bottom row) increases precision (study population C), as illustrated by the narrower 95% CI of the percentage error of clearance compared to the top row in figure 4.

In these simulations the percentage error of clearance remains within the -40 – 40% boundaries up to a body weight of 180kg, which covers the 99.5th body weight percentile. Frankly stricter boundaries on the prediction error of clearance of -25% – 25% would even be achievable with the current study design in this set of simulations after intravenous administration. Increased variability may however be anticipated for drugs that are for instance administered by oral administration. To ensure clarity between pharmacokinetics studies in various patient populations the -40 – 40% boundaries for the prediction error on clearance in individuals with obesity may be adopted.

Figure 3



A higher fold increase in clearance (FIC), defined as the ratio of typical clearance of an individual with body weight of 140kg and 70kg, has no noticeable influence on the precision of the estimation of clearance in the simulated studies as the median (horizontal black line) and 95% confidence interval of the percentage error (PE (%)) of clearance (shaded area) have a similar shape. The panels represent an increasing folds increase in clearance of 1.0 (no influence), 1.4 and 1.8, respectively with an IIV on CL of 20%.

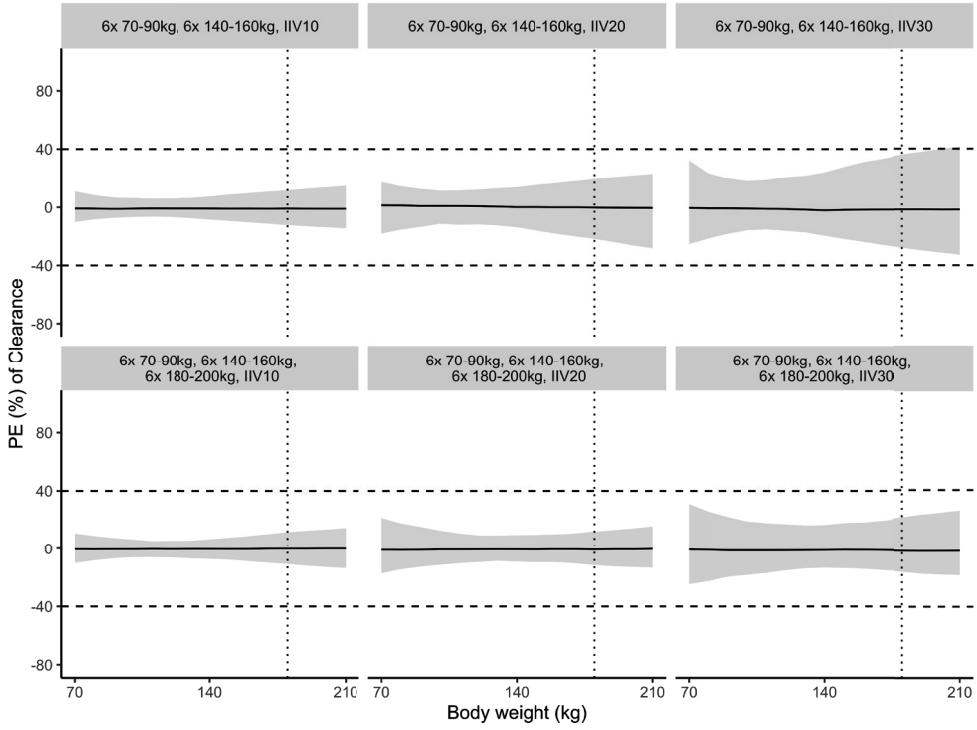
The horizontal dashed lines indicate the -40 – 40% boundaries for precision, the shaded 95% CI of the prediction error of clearance should remain within these lines up to the reference upper boundary body weight of 180kg.

Integrating sample size and prediction error

The simulations show that the sample size required to achieve sufficient precision for the described scenarios is generally lower than the sample size that is required to provide sufficient power. This is exemplified by a virtual drug with a fold increase in clearance of 1.5 and an IIV on CL of 25% for which study composition A yields sufficient precision (figure 3 & 4) although additional inclusion of individuals with body weight 180 – 200kg (to meet composition C) is needed to achieve a power of 80% (table 2). The IIV on CL in the pharmacokinetic model influences both the required sample size and the precision of the estimation of clearance while the fold increase in clearance in an individual of 140kg compared to 70kg influences the required sample size but not the precision of the estimation.

In the studies involving bariatric surgery patients described in chapter 2 and 3 the IIV on CL was 0% and 19% for fluconazole and ciprofloxacin, respectively. The methodology applied in these studies is thus capable of detecting a fold increase in clearance >1.25 with a power of >80%. A higher average body weight decreases the sample size that is required to achieve a power of 80%. The observed populations in chapter 2 and 3 consist of 8 normal weight individuals and 17 – 20 individuals with obesity with a body

Figure 4



An increase in inter-individual variability (IIV) on clearance decreases the precision of the estimated clearance as the 95% confidence interval of the percentage error (PE (%)) of clearance (shaded area) widens with increasing IIV. A Fold Increase in Clearance (FIC) of 1.3 was used in all of the tested scenarios in this figure. The top row represent a study population of 6 individuals with body weight 70 – 90kg and 6 individuals with obesity with body weight of 140 – 160kg (Composition A), the panels of the top row indicate an increasing IIV on clearance of 10%, 20% and 30%, respectively. The bottom row represents a study population of the top row with additional inclusion of 6 individuals with obesity with body weight of 180 – 200kg (composition C), the panels of the bottom row indicate an IIV on clearance of 10%, 20% and 30%, respectively.

The horizontal black line and shaded area indicate the median and 95% CI of the PE of clearance for each body weight within the 500 simulated studies. The horizontal dashed lines indicate the -40 – 40% boundaries for the 95% CI of the prediction error of clearance as a measure of accuracy. The vertical dashed line indicates the 180kg reference weight up to where the shaded area should remain within the horizontal boundaries.

weight up to 174kg for fluconazole and 212kg for ciprofloxacin, respectively. Therefore the minimal detectable fold increase in clearance in these studies may even be below the cut-off for clinical relevance of a fold increase in clearance of 1.25 given the high average body weight and the large sample size.

For the antimicrobials described in chapter 4, the IIV on clearance is >30% for 2 out of 19 (11%) agents which may have hampered detection of altered clearance in individuals with obesity as shown in table 2. For amoxicillin and amphotericin B, the antimicrobials with IIV on CL >30%, indeed no significant influence on clearance was detected. Although clearance may truly be unaltered in individuals with obesity for both drugs, no non-obese control population was included in both studies. Nevertheless a relatively wide range in body weights was observed in both studies with 88 – 151kg (average BMI 40.6kg/m^2) and 104 – 177kg (average BMI 45.9kg/m^2) for amoxicillin and amphotericin B, respectively.

The decrease in both the required sample size and PE(%) on CL with increasing body weight highlights the importance of observing a weight range that is as wide as possible. In order for these studies to be conclusive, some participants with a body weight of ideally >160kg and a control population of non-obese participants should be included.

Translating simulations into recommendations for trial design

To capture the influence of obesity on pharmacokinetics, the simulations need to be translated into practical recommendations for trial design. Several differences may occur between the simulated scenarios and reality. Most importantly, the body weight of participants with obesity is a given and is not necessarily within the body weight bands of 140 – 160kg and 180 – 200kg used in the simulations. Adapting inclusion criteria for individuals with obesity to individuals with an obesity phenotype and a body weight of >140kg allows inclusion of individuals with a body weight beyond these weight bands. Especially the inclusion of individuals with a body weight >160kg increases both power and precision of the study. The pool of individuals with obesity that is eligible for participation in PK-studies describing clearance in individuals with obesity is maximized using this approach.

A study into clearance in individuals with obesity may consist of initial inclusion of 6 normal weight participants and 6 individuals with obesity. The required sample sizes described in table 2, or a retrospective power calculation, can be used to judge if additional inclusion is warranted based on the identified fold increase in clearance and IIV on CL. For example: if the fold increase in clearance is <1.25 and the IIV on CL is <10% using composition A, no additional inclusion is needed based on table 2 and fixed dosing can be applied. In case the same analysis shows IIV on CL is around 20%, the true

fold increase in clearance is likely <1.5 but additional inclusion may be warranted to demonstrate whether the fold increase in clearance is >1.25 or not. In this last scenario a relevant increase in power can be achieved by aiming at inclusion of additional individuals with a body weight >160kg as a higher average bodyweight increases the statistical power (table 2).

Although there is a growing body of evidence supporting the notion that individuals with obesity should be recognized as a special patient population during drug development it remains to be determined who will be responsible for performing these studies. Moreover, it remains to be determined during which phase of pharmaceutical research these studies should be carried out. Population pharmacokinetics analysis is used as a tool to guide drug development and inform recommendations on therapeutic individualization. In some cases the need for post marketing requirements may even be alleviated[10]. Performing a small sample size pharmacokinetic study into the influence of obesity on pharmacokinetics during phase II, carried out by the pharmaceutical company developing the new drug, will yield vital information. The lessons learned from studies in individuals with obesity may also provide important insights for pharmaceutical companies themselves. If clearance is altered in individuals with obesity, weight based dosing should be the labeled dosing strategy whereas flat dosing should be the approach if no significant influence is found. When these studies are carried out at an early stage during drug development subsequent phases of research may be optimized as sufficient exposure can be assured while toxicity can be minimized for newly developed drugs. In this regard the first steps in the right direction have already been taken as for rivaroxaban individuals with a body weight up to 124kg were recruited during phase I while for apixaban individuals with a body weight up to 175kg were recruited during phase III[24, 25]. Moreover, efforts are made to predict the influence of obesity on pharmacokinetic parameters by taking drug properties like Log P and pK_a into account using Physiologically Based PharmacoKinetic (PBPK) modeling[26]. Future studies should point out to which extent PBPK models are able to adequately predict the influence of obesity on pharmacokinetic parameters.

In order to apply optimized treatment of infectious diseases in individual patients, it is necessary to understand the drivers of antimicrobial pharmacokinetic variability. To gain insight, studies in both otherwise healthy individuals with obesity and individuals with multi-morbidity are necessary. The most viable and logical approach with regard to obesity is to implement a two-stage approach. A pharmaceutical company evaluates if clearance is altered in individuals with obesity in a study population of otherwise healthy individuals with obesity during phase I or II. Subsequently an expansion to multimorbid individuals with obesity can be carried out by hospital pharmacists and clinicians during phase IV. In these studies the valuable information collected during

drug development can be taken into account. The population pharmacokinetic models can be enriched using therapeutic drug monitoring data from a larger number of patients or rich sampling data from a smaller number of individuals at a later stage. Based on this design, dose recommendations for individuals with morbid obesity and patients with multi-morbidity can be provided based on high quality data.

Conclusions

Pharmacokinetic changes can be induced by several (patho)physiological conditions. Given the strong exposure – response relationships for antimicrobial agents, optimization of exposure for this therapeutic class is paramount. The studies described in this thesis elucidate knowledge gaps regarding the drivers of pharmacokinetic variability of fluconazole and ciprofloxacin for individuals with obesity, ICU patients with obesity and hematological patients with mucosal barrier injury. As the global obesity prevalence increases rapidly, strategies for including these patients as a special patient population during drug development were explored.

The results of the studies presented in this thesis challenge common assumptions regarding the influence of weight on pharmacokinetics. Ciprofloxacin volume of distribution is not influenced by obesity while fluconazole volume of distribution did increase with body weight, especially in males. This necessitates an increased loading dose for male patients treated with fluconazole in order to shorten their time to reach target concentrations. The oral absorption of both drugs remained unaltered in individuals with obesity. Both ciprofloxacin clearance and volume of distribution remained uninfluenced by obesity although an increased clearance is commonly anticipated in these patients. The absence of an influence of obesity on clearance and volume of distribution was found both in individuals undergoing bariatric surgery and ICU patients with obesity. In ICU patients with obesity renal function is a viable predictor of ciprofloxacin clearance. In clinical practice doses are routinely reduced or dosing intervals are extended in patients with renal impairment, nevertheless increased doses may be needed in obese ICU patients with renal function >60ml/min/1.73m^2 to assure target attainment for pathogens with MIC >0.25mg/L.

For new drugs that currently reach the market there is still no guidance on how doses should be individualized in individuals with obesity although it is known that there is tremendous heterogeneity in the influence of body weight on pharmacokinetics which cannot be predicted using physiochemical properties. Therefore individuals with obesity should be recognized as a special patient population during drug development, preferably during phase I/II in which the influence of obesity on pharmacokinetics can be

determined. A study into clearance in individuals with obesity can be done by studying 6 – 12 individuals with obesity that are analyzed in conjunction with data from otherwise healthy non obese individuals. This information will prove to be vital in selecting the right dosing regimen, i.e. fixed dose when clearance is unaltered in individuals with obesity and a weight based regimen when clearances is altered in individuals with obesity. Moreover, the influence of body weight on volume of distribution can be investigated simultaneously which will yield vital information on the need for applying an individualized loading dose based on body weight.

Otherwise healthy individuals with obesity may still differ from the clinical population of individuals with obesity and/or multi-morbidity for instance with regard to age. Further examination of these subpopulations can be done by taking the previously determined influence of weight on pharmacokinetics into account. The population pharmacokinetic model can be extended to account for additional patient characteristics. This strategy aids to ultimately determine the most optimal dose for a broad spectrum of special patient populations.

Based on these studies, dose recommendations were developed for individuals with obesity, ICU patients with obesity and hematological patients with mucosal barrier injury. These studies revealed that a drug-by-drug evaluation of the influence of body weight on pharmacokinetics is necessary to provide accurate dose recommendations as variations within therapeutic classes prevent extrapolation to other drugs within the same class. Secondly, the importance of taking data from clinical patients into account is highlighted. After determining the influence of body weight on pharmacokinetics in otherwise healthy individuals with obesity, additional covariates may be of relevance to predict exposure in hospitalized patients with multimorbidity. Thirdly, the influence of obesity on pharmacokinetics can be determined up to a body weight of 180kg, covering 99.5% of the population of individuals with obesity, with sufficient precision using a small sample-size rich sampling pharmacokinetic study of 6 – 12 individuals with obesity.

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CHAPTER 8

8

Dutch Summary



Een verkenning van de farmacokinetische variabiliteit van antimicrobiële geneesmiddelen in mensen met (morbide) obesitas en patiënten met multimorbiditeit

Van de patiënten die in het ziekenhuis zijn opgenomen ondergaat ongeveer 1 op de 3 patiënten behandeling voor een infectieziekte[1]. Het antibioticum ciprofloxacine en het antischimmelmiddel fluconazol zijn veelgebruikte geneesmiddelen voor de behandeling van dergelijke aandoeningen. Micro-organismen die gevoelig zijn voor deze geneesmiddelen zijn Enterobacterales of Legionella in geval van ciprofloxacine en Candida, Cryptococcus *neoformans* of Cryptococcus *gattii* in geval van fluconazol[2, 3]. De uitscheiding van beide geneesmiddelen verloopt voornamelijk via de nieren wat aanpassing van doseerschema's vereist bij patiënten met een ernstig gestoorde nierfunctie[2, 3]. Na toediening van bijvoorbeeld een tablet is deze onderhevig aan absorptie, verdeling, omzetting en uitscheiding. Deze processen tezamen beschrijven de farmacokinetiek van een geneesmiddel. Het is bekend dat pathofysiologische aandoeningen zoals obesitas, ernstig ziek zijn of letsel aan de mucosa van het maagdarmkanaal de farmacokinetiek van een geneesmiddel kunnen beinvloeden[4-6]. Desondanks bestaat er voor zowel nieuwe als bestaande geneesmiddelen niet altijd een duidelijke richtlijn die voorschrijft hoe in specifieke gevallen de therapie aan te passen op het individu. Dit komt doordat deze aandoeningen geen specifieke aandacht krijgen binnen de registratiestudies voor nieuwe geneesmiddelen. Vooral mensen met obesitas verdienen erkenning als bijzondere patiëntpopulatie tijdens de ontwikkeling van geneesmiddelen. Enerzijds vanwege de onvoorspelbare invloed die obesitas heeft op de farmacokinetiek en anderzijds aangezien inmiddels ruim 13% van de wereldbevolking kampt met obesitas[7, 8].

Binnen het domein van de infectieziekten vertoont blootstelling aan antimicrobiële geneesmiddelen in plasma, of op de plaats van infectie, een sterke correlatie met het vinden van negatieve (bloed)kweken en genezing, vooral wanneer men hierbij de gevoeligheid van de ziekteverwekker voor het geneesmiddel in ogenschouw neemt[9]. Op basis van blootstelling-responsrelaties van het antimicrobiële geneesmiddel vindt individualisering van de therapie plaats in patiënten waarbij op basis van (patho) fysiologische aandoeningen een veranderde blootstelling te verwachten is. Op deze manier blijven zowel de effectiviteit als de veiligheid van de gekozen therapie optimaal geborgd.

Het onderzoek binnen dit proefschrift richt zich op het ophelderen van hoe obesitas, schade aan de mucosa bij patiënten met een hematologische aandoening, veranderde nierfunctie en opname op de IC de farmacokinetiek van ciprofloxacine en fluconazol beïnvloeden.

In **hoofdstuk 2** is bij personen met ernstige obesitas (BMI >40kg/m^2 of BMI >35kg/m^2 en comorbiditeiten) de farmacokinetiek van fluconazol zowel na orale als na intraveneuze toediening gekarakteriseerd. Hiervoor is een prospectief farmacokinetisch onderzoek uitgevoerd waarbij intensief bemonsterd is bij patiënten die een maagverkleining ondergingen (n=17) en een controlegroep van personen zonder obesitas (n=8, BMI <30kg/m^2). Deelnemers kregen een semi-simultane orale dosis van 400mg fluconazol, toegediend als capsule, gevolgd door een intraveneuze toediening van 400mg fluconazol in 2 uur. De geschatte biologische beschikbaarheid was 87,5% (met een 95% betrouwbaarheidsinterval van 43,9% - 98,4%). Toenemend lichaamsgewicht gaf zowel een hogere klaring (CL) als een groter verdelingsvolume (V_d). Geslacht bleek een significante voorspeller voor V_d aangezien deze bij mannen 27% groter is dan bij vrouwen. In onze onderzoekspopulatie verandert obesitas duidelijk de farmacokinetiek van fluconazol. Hierdoor lopen vooral mannen met ernstige obesitas (lichaamsgewicht >140kg) een risico om bij gangbare doseringen onvoldoende blootstelling te behalen. Er zijn alternatieve doseerregimes opgesteld om ook bij mannen met een lichaamsgewicht van >140kg voldoende blootstelling te bereiken.

In **hoofdstuk 3**, de tweede studie bij personen met obesitas, is de farmacokinetiek van ciprofloxacine gekarakteriseerd. Hierbij is wederom de farmacokinetiek na zowel orale als intraveneuze toediening geëvalueerd. Deelnemers met ernstige obesitas die een maagverkleining ondergingen kregen ciprofloxacine 500mg oraal (n=10) of 400mg intraveneus in 1 uur toegediend (n=10). De controlegroep van deelnemers zonder obesitas kregen een semi-simultane orale dosis van 500mg ciprofloxacine gevolgd door een intraveneuze toediening van 400mg in 1 uur startend 3 uur na inname van de orale dosis. Obesitas en lichaamsgewicht bleken niet voorspellend te zijn voor een veranderde klaring of distributievolume voor personen met een lichaamsgewicht van 57 – 212kg. Rekening houdend met literatuur die een verminderde weefselpenetratie naar spier- en vetweefsel beschrijft is de verwachting dat hogere plasmaconcentraties nodig zijn om in geval van een wekedelen infectie dezelfde weefselconcentratie te bereiken voor personen met en zonder obesitas[10]. Op basis van de data in plasma is echter geen bewijs gevonden van een invloed van obesitas op de farmacokinetiek van ciprofloxacine. Om die reden is het passend om bij patiënten met ernstig overgewicht de ciprofloxacine dosering te verhogen in geval van de behandeling van een infectie in weefsel met verminderde penetratie. Indien in het weefsel waar de infectie zich voordoet geen verminderde penetratie geanticipeerd is kunnen patiënten met en zonder obesitas een gelijke dosis krijgen.

In **hoofdstuk 4** zijn de resultaten van onze eigen studies naar de invloed van obesitas op de farmacokinetiek van antimicrobiële middelen (hoofdstukken 2 en 3) vergeleken met studies naar andere geneesmiddelen binnen een vergelijkbare patiënt populatie.

Evaluatie van 19 antimicrobiële middelen toonde een enorme variabiliteit in de invloed die obesitas heeft op klaring. Personen met obesitas lopen zowel risico op ontoereikende als overmatige blootstelling, in tegenstelling tot patiënten met nier- of leverfunctiestoornissen die voornamelijk risico lopen op overmatige blootstelling. Er zijn enerzijds geneesmiddelen met een op gewicht gebaseerd doseerregime gevonden die geen toegenomen klaring vertonen bij individuen met obesitas terwijl er anderzijds eveneens geneesmiddelen zijn met een gewichtsonafhankelijk doseerregime terwijl de geneesmiddelklaring wel toeneemt bij deze populatie. Dit resulteert in ontoereikende blootstelling in geval van gewichtsonafhankelijke doseerregimes en overmatige blootstelling in geval van op totaal lichaamsgewicht gebaseerde doseerregimes. Deze resultaten illustreren dat het vroegtijdig karakteriseren van de invloed van obesitas op de farmacokinetiek, en met name geneesmiddelklaring, van belang is om tot juiste doseerregimes te komen maar ook andere fasen van onderzoek te optimaliseren. Daarmee worden clinici direct nadat een geneesmiddel op de markt komt van essentiële informatie voorzien. Antimicrobiële therapie dient steeds meer op obesitas gerelateerde (patho)fysiologische veranderingen afgestemd te zijn. Om dit doel te bereiken moet de invloed van obesitas op de farmacokinetiek in een vroeg stadium tijdens de ontwikkeling van geneesmiddelen bestudeerd worden.

De invloed van obesitas op de farmacokinetiek van ciprofloxacine werd gekarakteriseerd in een relatief homogene populatie in hoofdstuk 3. De klinische populatie van patiënten met obesitas is wat comorbiditeiten echter heterogener waardoor mogelijk ook andere (patho)fysiologische processen, zoals een nierfunctiestoornis of opname op een intensive care (IC), veranderde farmacokinetiek verklaren. **In hoofdstuk 5** is de blootstelling aan ciprofloxacine geëvalueerd bij IC-patiënten met obesitas. Hiervoor zijn data van 34 IC-patiënten met obesitas (BMI >30kg/m^2) uit 4 eerdere studies naar de farmacokinetiek van ciprofloxacine bij IC-patiënten samengevoegd. In deze analyse zijn als controlepopulatie eveneens de gegevens na IV-toediening uit het onderzoek in hoofdstuk 2 meegenomen. Dit onderzoek toont aan dat nierfunctie, geschat volgens CKD-EPI, een goede voorspeller is voor de klaring van ciprofloxacine in de IC-populatie. Lichaamsgewicht bleek niet voorspellend te zijn voor een veranderde klaring of verdelingsvolume in IC-patiënten met obesitas. Op het populatie farmacokinetisch model gebaseerde simulaties tonen aan dat personen met een nierfunctie >60ml/min/1,73m^2 risico lopen op een suboptimale blootstelling bij een gangbare doseerstrategie wanneer een PK-PD target van AUC/MIC>125 bij een MIC van 0,25mg/L wordt gehanteerd.

De invloed van beschadiging aan de gastro-intestinale mucosale barrière op de farmacokinetiek van ciprofloxacine bij hematologie patiënten is onderzocht in **hoofdstuk 6**. Patiënten met een hematologische aandoening ontvangen ciprofloxacine

om tijdens neutropenie een infectie met een Gram-negatieve bacterie te voorkomen. Zij ontvangen hiervoor twee maaldaags een tablet met 500mg ciprofloxacine, ook wanneer zij schade aan de mucosa hebben terwijl niet duidelijk is of deze schade de orale opname van ciprofloxacine beïnvloedt. Om deze mogelijke invloed te onderzoeken zijn ciprofloxacine plasmaconcentraties op verschillende momenten na orale toediening geëvalueerd op verschillende dagen tijdens de behandeling. Gegevens verkregen na zowel orale als intraveneuze toediening van ciprofloxacine bij 28 gezonde vrijwilligers zonder schade aan de mucosa van het maag-dram kanaal dienden als controlegroep. De mate van schade aan het maagdarmkanaal is geobjectiveerd middels de Daily Gut Score (DGS), plasma citrulline concentratie en albumine. Gegevens van 47 patiënten met een grote verscheidenheid aan hematologische maligniteiten, verzameld op 0 – 30 dagen na aanvang van de chemotherapie waren beschikbaar. De tijd tot Cmax was langzamer bij hematologische patiënten vergeleken met gezonde vrijwilligers, hoewel er geen verband met de mate van schade aan het maagdarmkanaal (gedefinieerd als DGS of citrulline) is vastgesteld. Deze studie ondersteunt orale toediening van ciprofloxacine als Gram-negatieve profylaxe bij patiënten met een hematologische aandoening en matige schade aan het maagdarmkanaal.

De invloed van obesitas en multimorbiditeit op de farmacokinetiek van ciprofloxacine en fluconazol is binnen dit proefschrift in verschillende onderzoeken bestudeerd. De resultaten hiervan zijn in **hoofdstuk 7** samengevat en vanuit een breder perspectief besproken. Hierbij is gereflecteerd op de samenhang tussen, en methodologie van, de gekozen studies. Daarnaast is een standpunt ingenomen over op de plek die patiënten met obesitas zouden moeten hebben binnen het ontwikkelingstraject van nieuwe geneesmiddelen. Hierbij is een op dit standpunt gebaseerd onderzoeksontwerk verkend.

De manier waarop obesitas de farmacokinetiek van verschillende geneesmiddelen beïnvloedt is zeer heterogeen. Momenteel is deze invloed aan de hand van geneesmiddeleigenschappen zoals vetoplosbaarheid, eiwitbinding, ladingstoestand of bloed/plasma-ratio niet goed te voorspellen[11]. Bevindingen van geneesmiddel A zijn hierdoor niet te extrapoleren naar geneesmiddel B. Dit geldt zelfs voor geneesmiddelen die qua molecuulstructuur vergelijkbaar zijn, aangezien er binnen de therapeutisch klassen van echinocandines, cefalosporines, aminoglycosiden en triazolen belangrijke verschillen bestaan in de invloed die obesitas heeft op de farmacokinetiek van geneesmiddelen uit de betreffende klassen8.

Om de invloed van obesitas op de farmacokinetiek van ciprofloxacine en fluconazol zo zuiver mogelijk te karakteriseren is gebruik gemaakt van patiënten die voor een maagverkleining in het ziekenhuis waren. Een groot voordeel van het bestuderen van deze patiënten is dat handelingen die noodzakelijk zijn voor het uitvoeren van de studie

vooraf te plannen zijn. Hierdoor is het mogelijk om een brede gewichtsrange (tot aan een maximaal lichaamsgewicht van 218kg voor ciprofloxacine en 174kg voor fluconazol) te onderzoeken. Patiënten die in aanmerking komen voor een dergelijke operatie zijn, naast het feit dat ze obesitas hebben, relatief gezond. Daardoor komen andere factoren die karakterisering van de invloed van obesitas op de farmacokinetiek kunnen vertroebelen, zoals nier- en leverfunctiestoornissen of gebruik van interacterende comedicatie, weinig tot niet voor.

Daarnaast is in hoofdstuk 7 het belang van het verzamelen van data bij klinisch opgenomen patiënten benadrukt. In vergelijking met de relatief gezonde populatie individuen met obesitas die een maagverkleining ondergaan zijn bij de algemene klinische populatie belangrijke verschillen te verwachten in nierfunctie, leverfunctie, de invloed van IC-opname en leeftijd. Nadat in een relatief homogene populatie, zoals in hoofdstuk 2 en 3 beschreven, de invloed van obesitas op de farmacokinetiek is gekarakteriseerd kan uitbreiding van het populatie farmacokinetisch model plaatsvinden aan de hand van data uit de klinische praktijk.

Hiervoor is het essentieel om gedurende het analyseproces onderscheid te maken tussen de invloed van ziekte, comorbiditeit en comedicatie op de farmacokinetiek. De ernst van ziekte of comorbiditeit zijn te objectiveren aan de hand van biomarkers (kreatinine voor nierfunctie of citrulline voor mucositis van het maag-darm kanaal) of klinische scores (Sequential Organ Failure Assessment (SOFA score) voor IC-patiënten, Daily Gut Score (DGS) voor mucositis van het maagdarmkanaal). In de klinische populatie is, in tegenstelling tot de patiënten die een maagverkleining ondergaan, niet altijd te selecteren op patiënten die géén interacterende comedicatie gebruiken. Binnen de studie beschreven in hoofdstuk 6 gebruikte een groot deel van deze patiënten comedicatie (opiaten, maagzuurremmers, prokinetica of beta-blokkers) die de absorptie van ciprofloxacine kunnen versnellen, vertragen of verminderen. Tijdens het ontwikkelen van het farmacokinetisch model is het belangrijk om te evalueren of het model goed voorspelt voor gebruikers van interacterende comedicatie of patiënten met comorbiditeiten. Indien dit niet het geval is dient verfijning van het model plaats te vinden om ook voor deze karakteristieken juist te voorspellen. Via deze stapsgewijze aanpak is de invloed die verminderde nier- of leverfunctie, IC-opname, leeftijd, gebruik van interacterende comedicatie of maag-darmschade op de farmacokinetiek van het betreffende geneesmiddel te kwantificeren.

Ten derde is een potentieel ontwerp van registratiestudies verkend om tijdens de ontwikkeling van nieuwe geneesmiddelen de invloed van obesitas op de farmacokinetiek vast te stellen. Dit is belangrijk omdat inmiddels 13% van de wereldwijde populatie obesitas heeft, terwijl er voor geneesmiddelen die nieuw op de markt komen geen

doseerinformatie voor patiënten met obesitas beschikbaar is[1, 12]. In hoofdstuk 4 is uiteengezet hoe geneesmiddelen van elkaar verschillen met betrekking tot de invloed die obesitas op de farmacokinetiek heeft. Hierbij is gesteld dat een toename in klaring van <25% bij een individu van 140kg ten opzichte van een individu van 70kg niet klinisch relevant is. Bij een toename van 25 – 50% spreken we van een matige toename en bij >50% van een sterke toename.

Reeds beschikbare richtlijnen en handreikingen voor het ontwerp van geneesmiddelstudies in specifieke patiëntpopulaties zijn hiervoor vertaald naar de situatie waarin de invloed van obesitas op farmacokinetiek onderwerp van studie is[12, 13]. Binnen deze analyse is gefocust op wat de invloed is van verschillen in het lichaamsgewicht van de patiëntpopulatie, de grootte van de patiëntpopulatie, de mate van invloed van obesitas op de geneesmiddelklaring (toename in klaring door obesitas) en de variatie tussen patiënten met betrekking tot de snelheid waarmee zij geneesmiddelen klaren (interindividuele variabiliteit in klaring).

Uitgangspunt bij het ontwerp van een onderzoek is dat er een bepaalde mate van zekerheid is (veelal 80%) dat een effect dat in werkelijkheid aanwezig is binnen de ontworpen studie daadwerkelijk te detecteren is. De steekproefgrootte kiest men zodanig dat men deze mate van zekerheid verkrijgt. Om de praktische uitvoerbaarheid te borgen is uitgegaan van een beoogd maximum aantal proefpersonen met obesitas van 12 deelnemers.

De simulatiestudie leerde dat met een steekproef van 6 personen met obesitas met een lichaamsgewicht van 140 – 160kg en een controlegroep van 6 personen zonder obesitas een potentieel effect van obesitas op de farmacokinetiek detecteerbaar is wanneer de interindividuele variabiliteit in klaring <10% is. Bij een hogere interindividuele variabiliteit in klaring of een toename in klaring door obesitas die rondom de grens van klinische relevantie (±25%) ligt is aanvullende werving van personen met obesitas nodig om voldoende detecteerbaarheid te verkrijgen8. Om een relevante toename in detecteerbaarheid te bewerkstelligen is idealiter inclusie van personen met een hoger lichaamsgewicht (bijvoorbeeld 180 – 200kg) nodig. De steekproefgrootte die nodig is om een eventuele invloed van obesitas op de farmacokinetiek van een geneesmiddel te detecteren hangt enerzijds af van de mate waarin obesitas de geneesmiddelklaring beïnvloedt en anderzijds de mate van variatie in klaring tussen verschillende mensen.

Parallel is geëvalueerd of de invloed van obesitas op geneesmiddelklaring met de bovengenoemde studiepopulatie met voldoende juistheid te kwantificeren is. De mate waarin obesitas de geneesmiddelklaring beïnvloedt heeft geen effect op de juistheid van de analyse terwijl een hogere interindividuele variabiliteit in geneesmiddelklaring

wel een afname van de juistheid van de analyse brengt. Deze analyse toonde eveneens aan dat de invloed van de variabiliteit in geneesmiddelklaring tussen mensen op de detecteerbaarheid van de invloed van obesitas op geneesmiddelklaring sterker is dan de invloed op de juistheid van de analyse. De aanvullende inclusie die voor geneesmiddelen met een aanzienlijke interindividuele variabiliteit op geneesmiddelklaring (of matige invloed van obesitas op geneesmiddelklaring) nodig is om voldoende detecteerbaarheid te borgen zorgt tegelijkertijd dat de juistheid van de analyse voldoende is.

Bij de vertaling van bovengenoemde simulaties naar de werkelijkheid vallen enkele belangrijke punten op. Het gewicht van deelnemers met obesitas is een gegeven en kan daarom buiten de gesimuleerde gewichtscategorieën van 140 – 160kg en 180 – 200kg liggen. Door de inclusiecriteria te formuleren als "mensen met obesitas en een lichaamsgewicht van >140kg" is de populatie van mensen die in aanmerking komen voor deelname zo breed mogelijk. Wanneer de initiële inclusie van 6 individuen onvoldoende zekerheid geeft ten aanzien van de invloed van obesitas op de farmacokinetiek, is additionele inclusie mogelijk vereist. Om bij de additionele inclusie een relevante toename in statistische onderscheidingsvermogen te bereiken is het van belang om te sturen op werving van individuen met een zo hoog mogelijk lichaamsgewicht (idealiter >160kg).

Middels het beschreven studieontwerp is tijdens de ontwikkeling van nieuwe geneesmiddelen belangrijke kennis te verzamelen over de invloed van obesitas op de farmacokinetiek. Aanbevelingen voor dosisoptimalisatie bij patiënten met obesitas kunnen hiermee direct tijdens registratie van een nieuw geneesmiddel beschikbaar komen. Ziekenhuisapothekers en artsen kunnen vervolgens op basis van aanvullende data de meest optimale dosis voor individuen met obesitas en andere aandoeningen, zoals een lever- of nierfunctiestoornis, vaststellen. Het populatie farmacokinetisch model dient hiervoor verrijkt te worden met plasma concentratie – tijd profielen uit de klinische praktijk van patiënten met obesitas en relevante comorbiditeiten.

Concluderend is middels de onderzoeken die in dit proefschrift beschreven staan kennis vergaard over de invloed van obesitas, en multimorbiditeit in de vorm van IC-opname en obesitas of een hematologische aandoening en maag-darmschade op de farmacokinetiek van ciprofloxacine of fluconazol. Obesitas bleek niet van beïnvloed te zijn op de farmacokinetiek van ciprofloxacine terwijl zowel geslacht als gewicht van invloed zijn op de farmacokinetiek van fluconazol. Bij IC-patiënten met obesitas bleek eveneens dat obesitas geen invloed heeft op de farmacokinetiek maar dat nierfunctie wel voorspellend is voor de klaring van ciprofloxacine. Hematologische patiënten met maag-darmschade lieten een mild vertraagde orale absorptie van ciprofloxacine zien waaruit volgt dat de blootstelling aan ciprofloxacine niet anders is

dan bij gezonde vrijwilligers. Op basis van de populatie farmacokinetische modellen zijn doseeralgoritmes ontwikkeld voor beide geneesmiddelen.

Voor geneesmiddelen die nieuw op de markt komen verdient het includeren van personen met obesitas een sterke aanbeveling aangezien de invloed van obesitas op de farmacokinetiek heterogeen en onvoorspelbaar is. Door in de toekomst tijdens registratiestudies van nieuwe geneesmiddelen 6 – 12 personen met obesitas te bestuderen komt belangrijke informatie over de invloed van obesitas op de farmacokinetiek op een vroeg moment beschikbaar. Clinici kunnen hiermee de juiste dosering kiezen voor patiënten met obesitas.

Met de binnen dit proefschrift opgedane kennis zijn enkele kennishiaten ten aanzien van de drijvende krachten achter de farmacokinetische variabiliteit van antimicrobiële geneesmiddelen beschreven. Dit onderzoek draagt hiermee bij aan het optimaliseren van de behandeling met fluconazol en ciprofloxacine voor bij patiënten met obesitas of multimorbiditeit in de vorm van obesitas en IC-opname of een hematologische maligniteit en maag-darmschade.

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Part V

Appendices

Curriculum vitae

Koen van Rhee was born on September 11th 1989 in Oldenzaal, the Netherlands. After his graduation from the Carmel Lyceum in Oldenzaal in 2007, he studied Pharmacy at the Rijks University Groningen. In 2014 he graduated with a Master in Pharmacy. After his graduation he worked as a pharmacist in the University Medical Center Groningen and the Amsterdam University Medical Center (location VUmc and AMC). In 2015 he started a residency in hospital pharmacy at Tergooi Medical Center, Hilversum. He combined this residency with a PhD research project carried out under the supervision of Prof. dr. C.A.J. Knibbe, Prof. dr. R.J.M. Brüggemann and dr. P.D. van der Linden. Koen registered as a hospital pharmacist in 2019 and holds a position as a hospital pharmacist in the St. Jansdal hospital, Harderwijk. He currently lives in Amersfoort with Wytske and their two sons, Bob and Laurens.

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Dankwoord – acknowledgements

De afronding van dit proefschrift was niet mogelijk geweest zonder de hulp van vele anderen, bij enkelen wil ik in het bijzonder stilstaan. Allereerst hebben de deelnemers aan de verschillende onderzoeken het verzamelen van klinische data mogelijk gemaakt door tijdens een voor hen zeer belangrijke behandeling, een maagverkleining, IC opname of behandeling voor leukemie, mee te doen aan wetenschappelijk onderzoek. Daarvoor ben ik hen dankbaar.

Catherijne, bedankt voor de fijne samenwerking. Je hebt een enorm enthousiasme voor het doen van onderzoek, hierdoor kon ik na onze besprekingen steeds met frisse moed verder. Met enkele vragen weet je tot de kern te komen om vanuit daar analyse en resultaten nog verder aan te scherpen of deze net wat handiger te presenteren, daar heb ik enorm van geleerd. Roger, met jouw expertise op PK/PD gebied hebben we de translatie van onze resultaten naar de patiënt en de klinische context extra vorm kunnen geven. Meermaals kwam je met interessante invalshoeken en aanknopingspunten voor vervolgonderzoek, bedankt daarvoor. Paul, zowel tijdens mijn opleiding als onderzoek heb ik veel van je geleerd. Jouw enthousiasme voor infectieziekten en antibiotica zijn besmettelijk gebleken. Je me de kans gegeven om met PK/PD-modelling mijn eigen domein te kiezen maar tegelijkertijd is het erg leuk om desondanks grotendeels op hetzelfde antibioticum te promoveren!

Naast mijn promotieteam wil ik alle coauteurs bedanken voor de interessante discussies en gedeelde expertise en ervaring. Enkelen wil ik specifiek bedanken. Cornelis, je hebt me geduldig de fijne kneepjes van zowel de praktische uitvoer van het onderzoek bij de bariatrie als de eerste stappen van de data-analyse binnen NONMEM en R geleerd. Je tip om voor verdieping een summerschool in Minneapolis te volgen leidde ook nog eens tot een mooie ervaring.

Dear Lu, the time we spent together in the hospital for the fluconazole study was really enjoyable. I'm now fully aware of the importance of allowing full oral absorption before starting the IV administration within a semi-simultaneous study design. Thank you for the collaboration and especially the meticulous data analysis.

Suzanne, het was leuk om de handen ineen te slaan voor de studie naar de invloed van mucositis op de orale absorptie van ciprofloxacine waar we los van elkaar al mee bezig bleken te zijn. Jouw klinische blik als arts was hierbij van grote waarde.

Beste Eric van Dongen, Sylvia Bliemer, Brigitte Samsom, Angela Colbers en medewerkers van het CRCN, jullie hulp heeft enorm geholpen tijdens de inclusie van patiënten in het st. Antonius ziekenhuis en het Radboud UMC. Bedankt voor deze prettige samenwerking.

Deze onderzoeken hebben grotendeels plaatsgevonden tijdens mijn opleiding in Tergooi MC. Graag wil ik de ziekenhuisapothekers, A(N)IOS en apotheker-onderzoekers bedanken voor alles wat ik geleerd heb, de ruimte om onderzoek te doen en, niet onbelangrijk, de gezellige tijd. De flexibiliteit wanneer er op het laatste moment diensten of afspraken verschoven moesten worden om ruimte te maken voor een deelnemer aan onderzoek waren erg fijn.

Jill en Luuk, mede dankzij jullie vliegen menig werkdag of culinaire uitstapjes rap voorbij. Fijn om jullie straks ook bij de verdediging aan mijn zijde te hebben.

Als laatste bedank ik graag mijn vrienden en familie voor alle interesse en hulp in de afgelopen jaren. In het bijzonder wil ik mijn ouders Nico en Mariët noemen omdat jullie altijd liefdevol klaarstaan.

Lieve Wytske, je bent er altijd voor me en steunt me onvoorwaardelijk in de dingen die belangrijk zijn, bedankt daarvoor. Bob en Laurens, de vrolijkheid die steeds uit jullie ogen straalt is prachtig om te zien en dat geeft enorm veel energie.