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

Rhee, K.P. van

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.

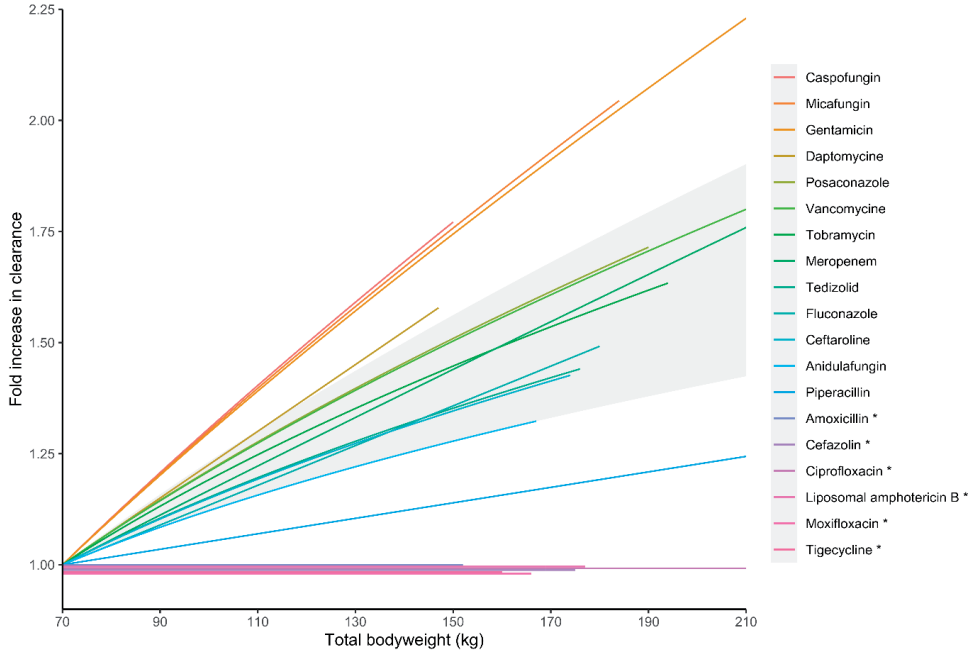
The population of hospitalized patients with multimorbidity is heterogeneous compared to the bariatric surgery population. In patients with multimorbidity as shown in this thesis, pharmacokinetic alterations may be caused by clinical interventions (e.g. fluid resuscitation or medication), disease and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

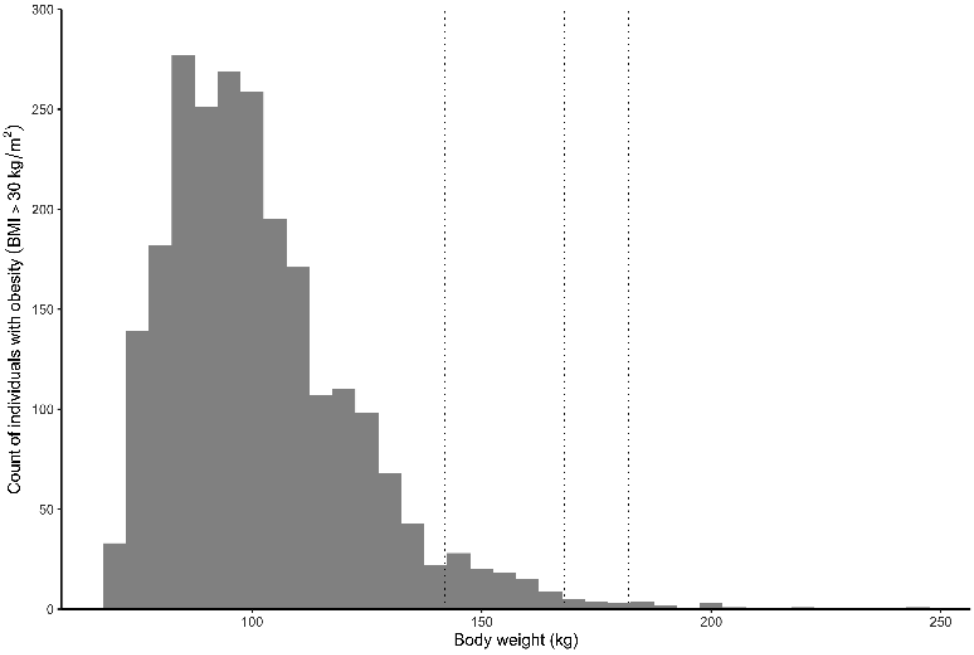
Prediction error of clearance

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

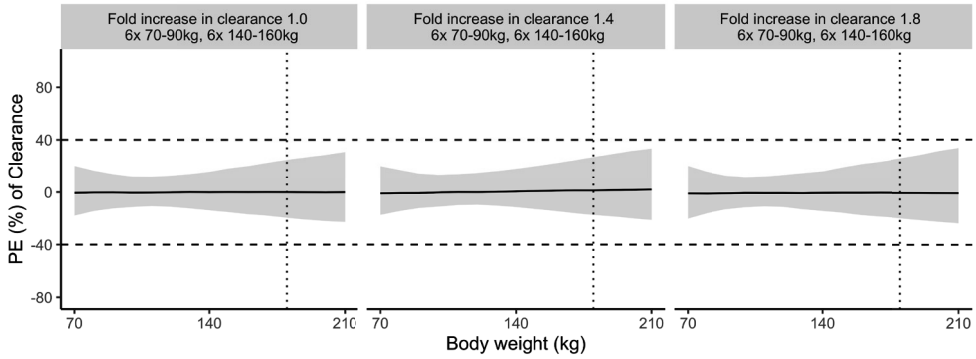
Equation 2b: $Estimated\ CL_i = \theta_{CL} * (\frac{WT}{70\ kg})^{\theta_{\exp CL}}$

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%.

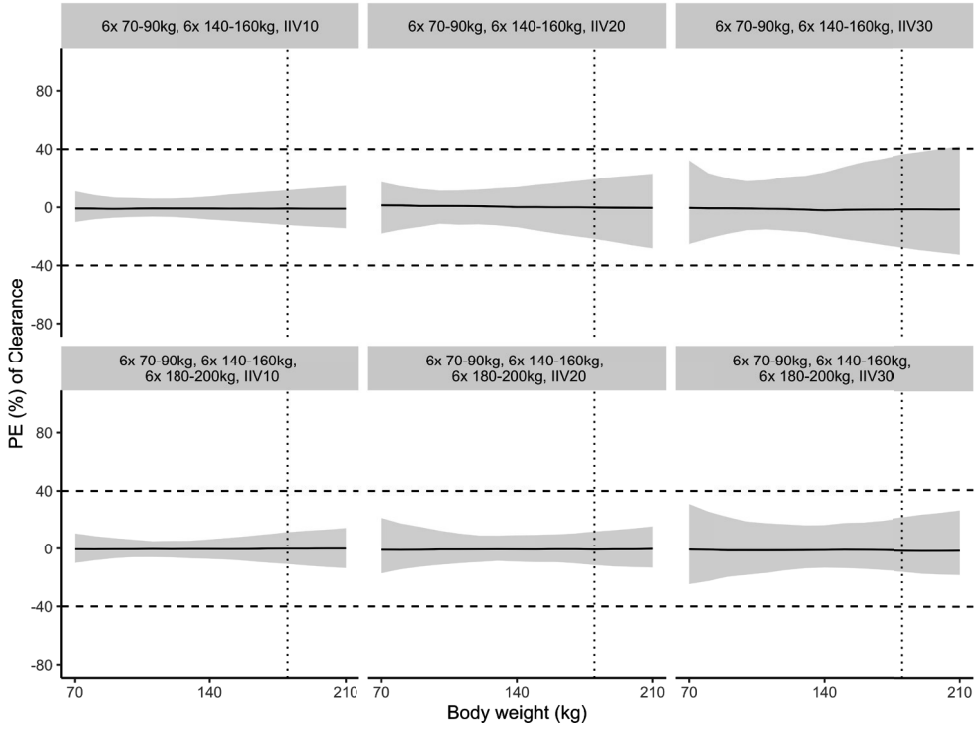
The horizontal dashed lines indicate the -40 – 40% boundaries for precision, the shaded 95% CI of the prediction error of clearance should remain within these lines up to the reference upper boundary body weight of 180kg.

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.

References

1 vans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247.

2 Fluconazole access data. Food and drug administration, 28/02/2019. Accessed 4/3/2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019949s065,020090s047lbl.pdf

3 Ciprofloxacin access data. Food and Drug Administration, 30/7/2016. Accessed 4/3/2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019537s086lbl.pdf

4 Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic Alterations Associated with Critical Illness. Clin Pharmacokinet. 2023 Feb;62(2):209-220.

5 Smit C, De Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. Expert Opin Drug Metab Toxicol. 2018 Mar;14(3):275-285.

6 da Silva Ferreira AR, Märtson AG, de Boer A, Wardill HR, Alffenaar JW, Harmsen HJM, Tissing WJE. Does Chemotherapy-Induced Gastrointestinal Mucositis Affect the Bioavailability and Efficacy of Anti-Infective Drugs? Biomedicines. 2021 Oct 4;9(10):1389.

7 Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, Jarlier V, Nathwani D, Goossens H; Global-PPS network. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018 Jun;6(6):e619-e629.

8 Nielsen EI, Friberg LE. Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Pharmacol Rev. 2013 Jun 26;65(3):1053-90.

9 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 Mar;25(3):354-8.

10 Population pharmacokinetics, Guidance for Industry. Food and Drug administration, 28/2/2022. Accessed 6/3/2024 https://www.fda.gov/media/128793/download

11 Pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing, Guidance for industry. Food and Drug Administration, 3/2024. Accessed 22/3/2024. https://www.fda.gov/media/78573/download

12 van Rhee KP, Knibbe CAJ, van der Linden PD, Brüggemann RJM. Patients with Obesity Should be Recognised as a Special Patient Population During Drug Development of Antibacterial and Antifungal Agents; A Call to Action. Clin Pharmacokinet. 2024 Jan;63(1):1-12.

13 Vong C, Bergstrand M, Nyberg J, Karlsson MO. Rapid sample size calculations for a defined likelihood ratio test-based power in mixed-effects models. AAPS J. 2012 Jun;14(2):176-86.

14 Wasmann RE, Ter Heine R, van Dongen EP, Burger DM, Lempers VJ, Knibbe CA, Brüggemann RJ. Pharmacokinetics of Anidulafungin in Obese and Normal-Weight Adults. Antimicrob Agents Chemother. 2018 Jun 26;62(7):e00063-18.

15 Chen L, van Rhee KP, Wasmann RE, Krekels EHJ, Wiezer MJ, van Dongen EPA, Verweij PE, van der Linden PD, Brüggemann RJ, Knibbe CAJ. Total bodyweight and sex both drive pharmacokinetic variability of fluconazole in obese adults. J Antimicrob Chemother. 2022 Jul 28;77(8):2217-2226.

16 Busse D, Simon P, Schmitt L, Petroff D, Dorn C, Dietrich A, Zeitlinger M, Huisinga W, Michelet R, Wrigge H, Kloft C. Comparative Plasma and Interstitial Tissue Fluid Pharmacokinetics of Meropenem Demonstrate the Need for Increasing Dose and Infusion Duration in Obese and Non-obese Patients. Clin Pharmacokinet. 2022 May;61(5):655-672.

17 Smit C, Wasmann RE, Wiezer MJ, van Dongen HPA, Mouton JW, Brüggemann RJM, Knibbe CAJ. Tobramycin Clearance Is Best Described by Renal Function Estimates in Obese and Non-obese Individuals: Results of a Prospective Rich Sampling Pharmacokinetic Study. Pharm Res. 2019 May 30;36(8):112. doi: 10.1007/s11095-019-2651-2. Erratum in: Pharm Res. 2020 Jan 9;37(2):32.

18 Smit C, Wasmann RE, Goulooze SC, Wiezer MJ, van Dongen EPA, Mouton JW, Brüggemann RJM, Knibbe CAJ. Population pharmacokinetics of vancomycin in obesity: Finding the optimal dose for (morbidly) obese individuals. Br J Clin Pharmacol. 2020 Feb;86(2):303-317

19 Wasmann RE, Smit C, van Donselaar MH, van Dongen EPA, Wiezer RMJ, Verweij PE, Burger DM, Knibbe CAJ, Brüggemann RJM. Implications for IV posaconazole dosing in the era of obesity. J Antimicrob Chemother. 2020 Apr 1;75(4):1006-1013.

20 Smit C, Wasmann RE, Goulooze SC, Hazebroek EJ, Van Dongen EPA, Burgers DMT, Mouton JW, Brüggemann RJM, Knibbe CAJ. A Prospective Clinical Study Characterizing the Influence of Morbid Obesity on the Pharmacokinetics of Gentamicin: Towards Individualized Dosing in Obese Patients. Clin Pharmacokinet. 2019 Oct;58(10):1333-1343

21 Wasmann RE, Smit C, Ter Heine R, Koele SE, van Dongen EPH, Wiezer RMJ, Burger DM, Knibbe CAJ, Brüggemann RJM. Pharmacokinetics and probability of target attainment for micafungin in normal-weight and morbidly obese adults. J Antimicrob Chemother. 2019 Apr 1;74(4):978-985.

22 Overweight & Obesity. Centers for Disease Control and Prevention (CDC), 21/9/2023. Accessed 6/3/2024 https://www.cdc.gov/obesity/index.html

23 Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats, Centers for Disease Control and Prevention. 2020. Updated February 8, 2021. Accessed march 15th 2024. www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm

24 Food and Drug Administration – Rivaroxaban clinical pharmacology review. Apr 2009, accessed may 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406orig1s000clinpharmr.pdf

25 Food and Drug administration – apixaban clinical pharmacology review. Feb 2012, accessed may 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155orig1s000clinpharmr.pdf

26 Berton M, Bettonte S, Stader F, Battegay M, Marzolini C. Physiologically Based Pharmacokinetic Modelling to Identify Physiological and Drug Parameters Driving Pharmacokinetics in Obese Individuals. Clin Pharmacokinet. 2023 Feb;62(2):277-295.