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

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CHAPTER 3

# 3

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

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## 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**

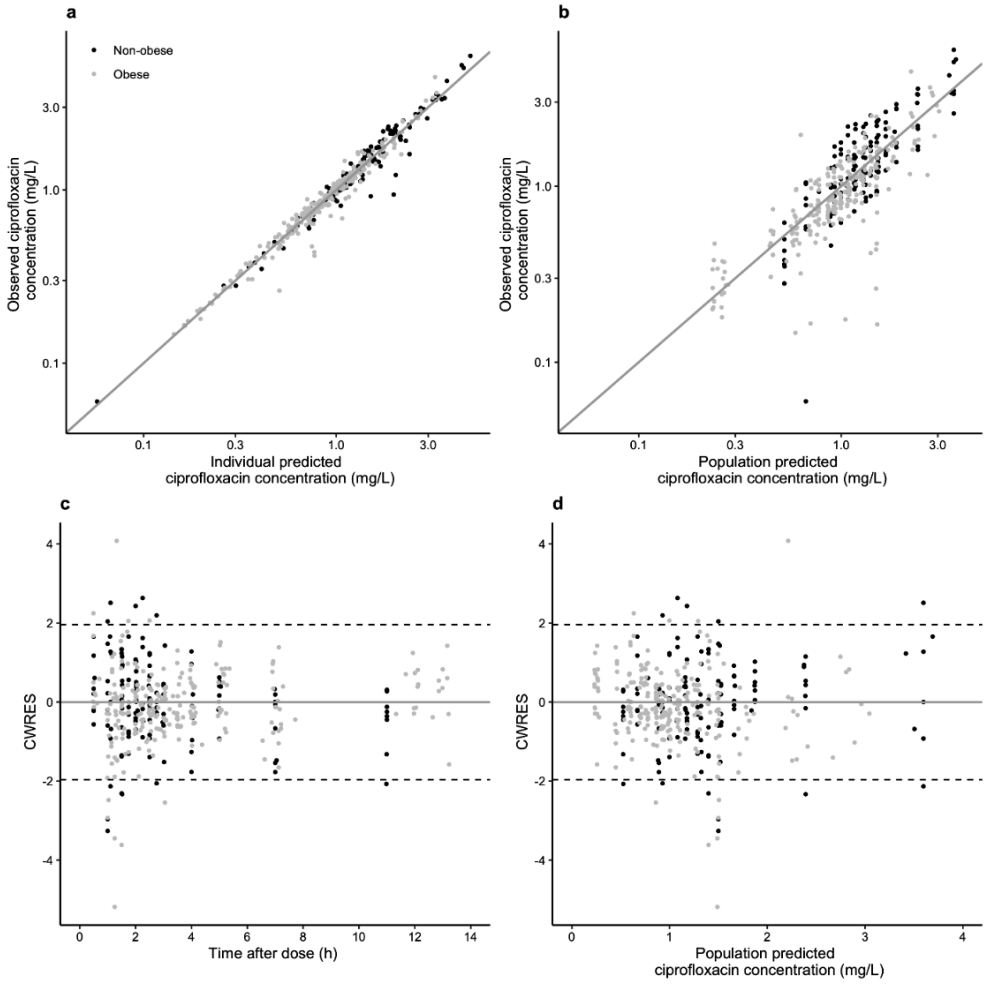
| | Morbidly Obese (n=20) | Non-obese (n=8) |
|---|---|---|
| Total body weight (kg) | 141 (42) [107-212] | 66 (14) [57 – 85] |
| Lean body weight (kg) | 70 (18) [52-102] | 49 (20) [38-66] |
| BMI (kg/m$^2$) | 45 (8.3) [39-58] | 21 (4.2) [19-25] |
| Male sex (%) | 50 | 50 |
| Age (years) | 49 (18) [27 – 59] | 25 (3) [20 – 51] |
| Race (n) | Kaukasian 19<br>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]<br>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%)*

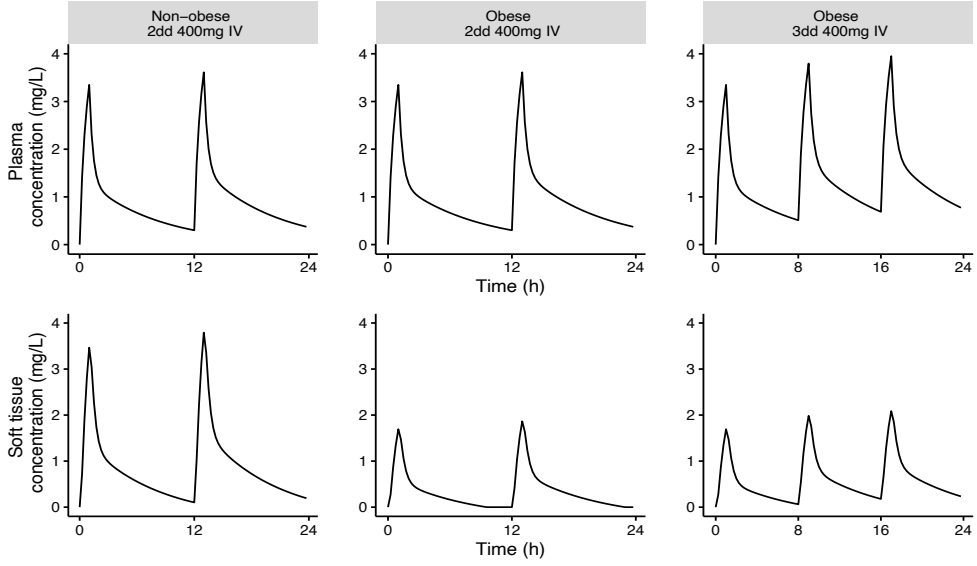
The soft tissue concentrations in obese and non-obese patients taken from literature were best described by adding a tissue compartment with first order distribution to tissue and combined zero- and first-order elimination from tissue[8]. To capture the

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 $\theta_{mean}$ and the random variable $\eta_i$ (eta) for the $i^{th}$ individual from a normal distribution with a mean of 0 and estimated variance of $\omega^2$.

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



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 $\sigma^2$. 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.

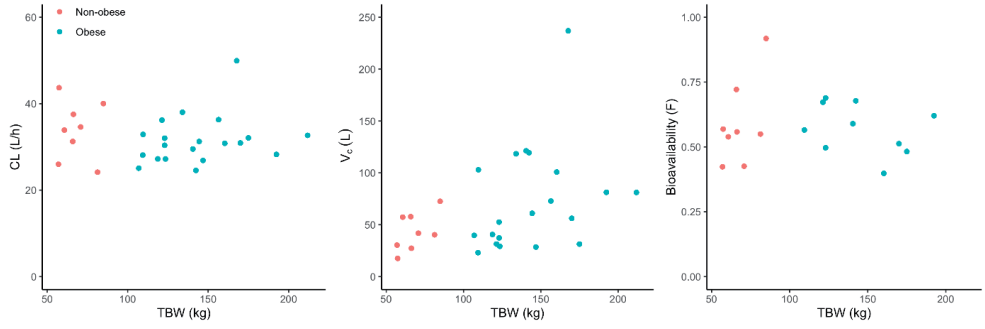
$$P_i = P_p \times (COV_i / COV_{standard})^X \qquad (3)$$

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

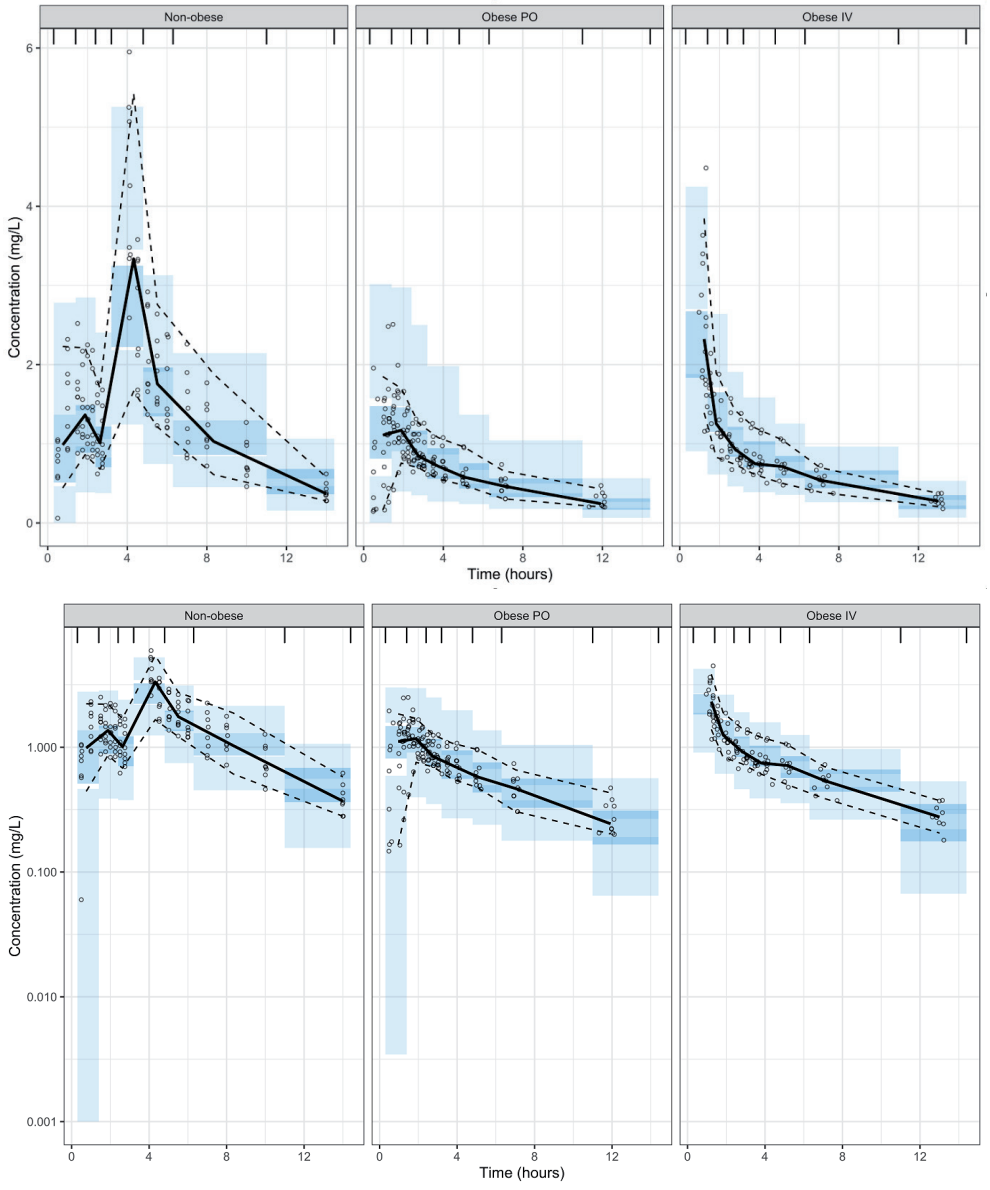
Figure 1 shows the Empirical Bayes Estimates on clearance and volume of distribution versus total body weight. Clearance shows no trend with bodyweight. Central volume of distribution does show a small trend with TBW, but inclusion of TBW as a covariate on $V_c$ did not reach statistical significance.

**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

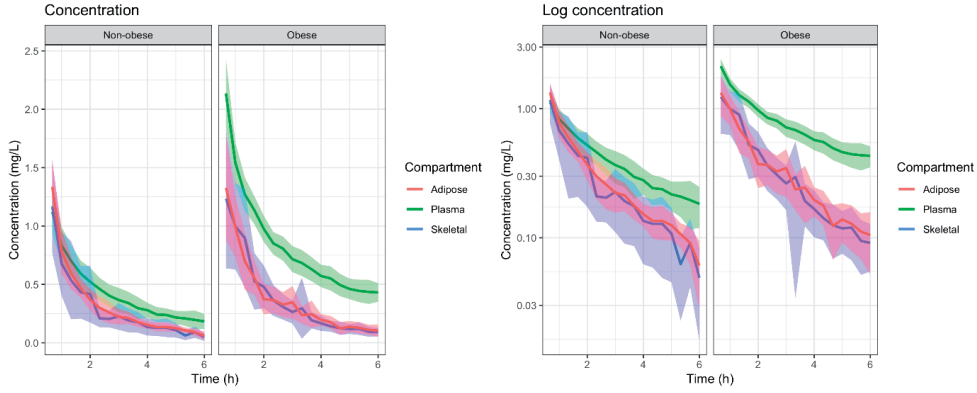
To account for reduced ciprofloxacin tissue penetration in obese patients as was reported by Hollenstein *et al.*, the ciprofloxacin model was extended with tissue concentrations from literature to explore dosing regimens leading to similar ciprofloxacin exposure in skin and soft tissue for non-obese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

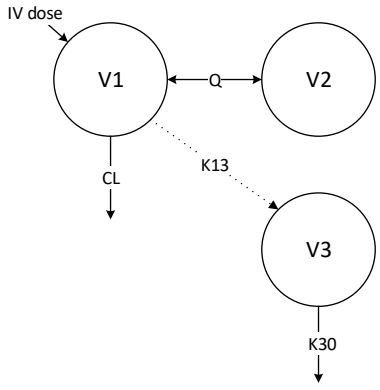
### Model building

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*

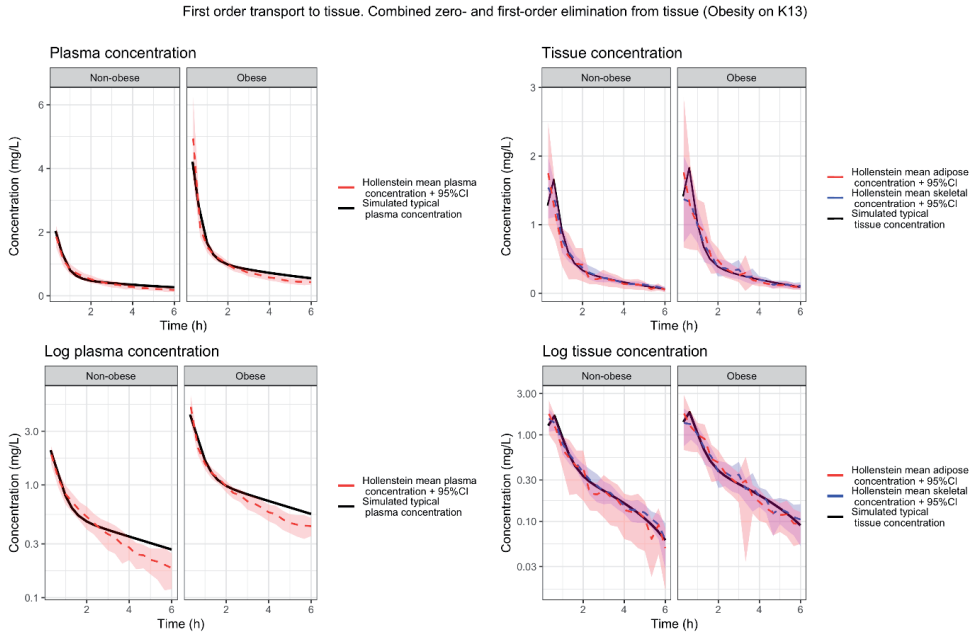
### Tissue penetration ratio

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.

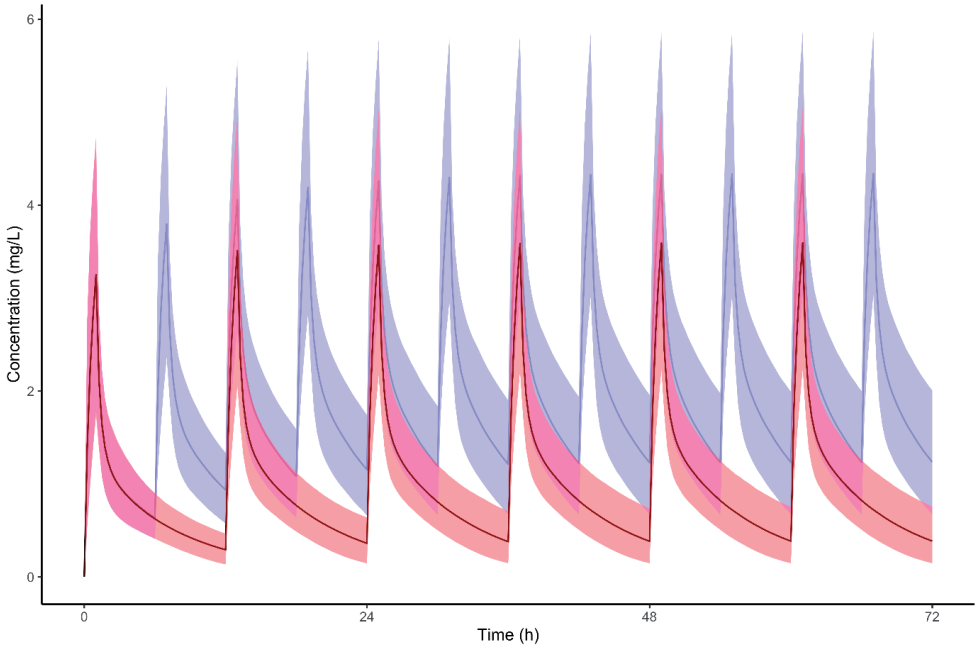
**Table S4: Exposure in plasma and tissue on day 3**

| | 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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