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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Background and Objective Ciprofloxacin is a fluoroquinolone used for empirical and targeted therapy of a wide range of infections. Despite the increase in obesity prevalence, only very limited guidance is available on whether the ciprofloxacin dose needs to be adjusted when administered orally or intravenously in (morbidly) obese individuals. 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.

Methods (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 ($n = 8$). All participants underwent rich sampling (11–17 samples) for 12 h after administration. Non-linear mixed-effects modelling and simulations were performed to evaluate ciprofloxacin exposure in plasma. Prior data from the literature were subsequently included in the model to explore exposure in soft tissue in obese and non-obese patients.

Results Overall, 28 participants with body weights ranging from 57 to 212 kg were recruited. No significant influence of body weight on bioavailability, clearance or volume of distribution was identified (all $p > 0.01$). Soft tissue concentrations were predicted to be lower in obese individuals despite similar plasma concentrations compared with non-obese individuals.

Conclusion 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. In the treatment of infections in tissue where impaired ciprofloxacin penetration is anticipated, higher dosages may be required.

Trial Registration Registered in the Dutch Trial Registry (NTR6058).

1 Introduction

Ciprofloxacin is a fluoroquinolone that is 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 administered 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 transepithelial 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 such as route of elimination, hepatic extraction ratio, involvement of transporters, protein binding, ionisation 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

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Key Points

There is currently no consensus on how ciprofloxacin should be administered in (morbidly) obese individuals.

In this study of 20 morbidly obese and 8 non-obese individuals with body weights ranging from 57 to 212 kg and normal renal function, we found that body weight was not associated with changes in bioavailability, clearance, or volume of distribution in a two-compartment model with transit compartment absorption.

Ciprofloxacin dose adjustment based on body weight is not warranted for empirical treatment of infections. Nevertheless, higher dosages may be required if penetration in the target tissue is known to be impaired in obese individuals, as is the case for skin and soft tissue infections.

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 individuals, and 0.85 for non-obese versus 0.46 for obese individuals 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 administer ciprofloxacin in obese patients when administered 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 previously reported 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.

2 Materials and Methods

2.1 Participants

Eight healthy (BMI < 25 kg/m^2) and 20 (morbidly) obese individuals (BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with comorbidities) 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. cytochrome P450 [CYP] 3A4 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 Centre, 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 in the study.

2.2 Study Procedures

Obese individuals received a single dose of either 500 mg oral ciprofloxacin or 400 mg intravenous ciprofloxacin. Obese patients were assigned intravenous or oral 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 h before surgery to allow for complete absorption. A full concentration-time curve containing 11 (intravenous) or 15 (oral) samples per individual was collected over a 12-h period after administration.

Non-obese participants received 500 mg orally followed by 400 mg intravenously infused over 1 h, starting 3 h after the oral dose. For non-obese participants, 17 samples (8 after oral administration and 9 after intravenous administration) were collected over 16 h beginning after oral administration (see Online Resource 1 for the sampling scheme).

Samples were collected in EDTA tubes, stored on ice, centrifuged at 1900 g for 5 min and stored at − 80°C until analysis. Total ciprofloxacin concentrations were analysed using a validated ultra-performance liquid chromatography–tandem mass spectrometric assay (Waters Corporation, Milford, MA, USA) with a concentration range of 0.050–10 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, and the corresponding between-day %CV were 3.21% and 2.46%, respectively.

For each participant, data on weight, height, age, sex, and duration and history of obesity were recorded. Serum creatinine was measured and 24 h urine was collected during the day of the study to calculate the measured glomerular filtration rate (mGFR). Serum creatinine-based estimations of GFR were obtained using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [10] and CKD-EPI$_{\text{de-indexed}}$ (de-indexed for body surface area [BSA] by

multiplying CKD-EPI by BSA/1.73), Modifications of Diet in Renal Disease (MDRD) [11] and $MDRD_{de\text{-}indexed}$ (de-indexed for BSA), and Cockcroft–Gault (CG; based on TBW and lean body weight [LBW] for obese individuals, and 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].

2.3 Pharmacokinetic Analysis

All concentration-time data were analyzed using 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], and a one- and two-compartment model with first-order elimination was tested to describe ciprofloxacin distribution. Log-normal distribution of interindividual variability was assumed. Proportional, additive and combined residual error models were evaluated. A p-value < 0.05, representing a 3.84 decrease in objective function value (OFV) for one 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, $CKD\text{-}EPI_{de\text{-}indexed}$, CG_{TBW} and CG_{LBW} 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 interindividual variability, evaluation of goodness-of-fit (GOF) plots, and Empirical Bayesian Estimate versus potential covariates. Internal model validation was performed using visual predictive checks (VPCs). Model robustness and parameter precision were assessed using sampling importance resampling with 5000 samples and 1000 resamples [19]. For further details on the model building, see Online Resource 1.

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 the literature through plot digitization [8]. Parameters describing transport to and elimination from the soft tissue were estimated as described in Online Resource 1.

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 intravenous infusions of ciprofloxacin 400 mg two to four times daily.

3 Results

3.1 Patients and Data

Twenty (morbidly) obese participants with a median (interquartile range [IQR]) body weight of 141 (42) kg and median (IQR) mGFR of 148 (62) mL/min, and eight healthy individuals with a median (IQR) body weight of 66 (14) kg and median (IQR) mGFR of 129 (17) mL/min were included. Patient demographics are described in Table 1. A total of 392 plasma samples were obtained; one sample (0.26%) was below the quantification limit at 30 min after oral administration and was excluded from the analysis.

3.2 Pharmacokinetic Model

The observed data was best described using a two-compartment model with first-order elimination, interindividual variability on clearance, central and peripheral volume of distribution, intercompartmental clearance and a proportional error model. 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 ($p > 0.01$, OFV reduced by 6.2). In the model with TBW as a covariate on CL, an exponent of only − 0.06 (relative standard error 194%) was found without an improvement of fit ($p > 0.05$, OFV reduced by 0.3) [see Fig. 1 in Online Resource 1]. The final model adequately described the observed data, as illustrated in Fig. 1. The conditional weighted residuals indicate no model misspecification, as distribution of residuals is homogenous over time and concentration (for VPCs, see Fig. 2 in Online Resource 1). Parameter estimates of the final model are shown in Table 2.

The soft tissue concentrations in obese and non-obese patients taken from the literature [8] were best described by adding a tissue compartment with first-order distribution to tissue and combined zero- and first-order elimination from tissue. 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 ($p < 0.001$, OFV reduced by 174). The results of model building and validation are presented in Online Resource 1.

Table 1 Patient demographics

Variable	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*)	Caucasian: 19 Asian: 1	Caucasian: 8
mGFR 24-h urine (mL/min)	148 (62) [100–254]	129 (17) [99–208]
Indexed CKD-EPI (mL/min/1.73 m^2)	100 (18) [72–119]	107 (8) [84–118]
De-indexed CKD-EPI (mL/min)[a]	140 (29) [86–209]	113 (21) [80–139]
Indexed MDRD (mL/min/1.73 m^2)	93 (21) [65–133]	92 (6) [74–103]
De-indexed MDRD (mL/min)[a]	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]	NA

BMI body mass index, *mGFR* measured glomerular filtration rate, *TBW* total body weight, *LBW* lean body weight (12), *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *MDRD* Modifications of Diet in Renal Disease, *NA* not available, *IQR* interquartile range

Data are expressed as median (IQR) [range] unless specified otherwise

[a]De-indexing was performed by multiplying the original CKD-EPI or MDRD by body surface area/1.73

To evaluate the commonly used dosing regimen of two or three times daily intravenous infusions of ciprofloxacin 400 mg, simulated ciprofloxacin concentration-time profiles in plasma for obese and non-obese individuals are shown in Fig. 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 reported by Hollenstein 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 intravenous infusions of ciprofloxacin 400 mg. After twice-daily intravenous infusions of 400 mg, the typical AUC_{tissue} on day 3 was 24 mg*h/L for non-obese individuals and 10 mg*h/L for obese individuals.

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 intravenous dose of 400 mg, a three-times-daily dosing regimen yields an AUC_{tissue} of 18 mg*h/L, and a four times daily regimen yields an AUC_{tissue} of 26 mg*h/L, for a typical obese patient on day 3 of therapy. While both regimens result in exposure in soft tissue that is similar to non-obese patients after a twice daily 400 mg intravenous regimen, higher plasma concentrations are observed due to the absence of an influence of weight on clearance in obese compared with non-obese individuals (see Fig. 6 in Online Resource 1).

4 Discussion

Collecting prospective data on the pharmacokinetics of antibiotics such as 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 TBWs over a large weight range (57–212 kg). 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 gastrointestinal 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% confidence interval [CI] 49–66%) that we report is comparable with the 56–77% that is reported in the 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].

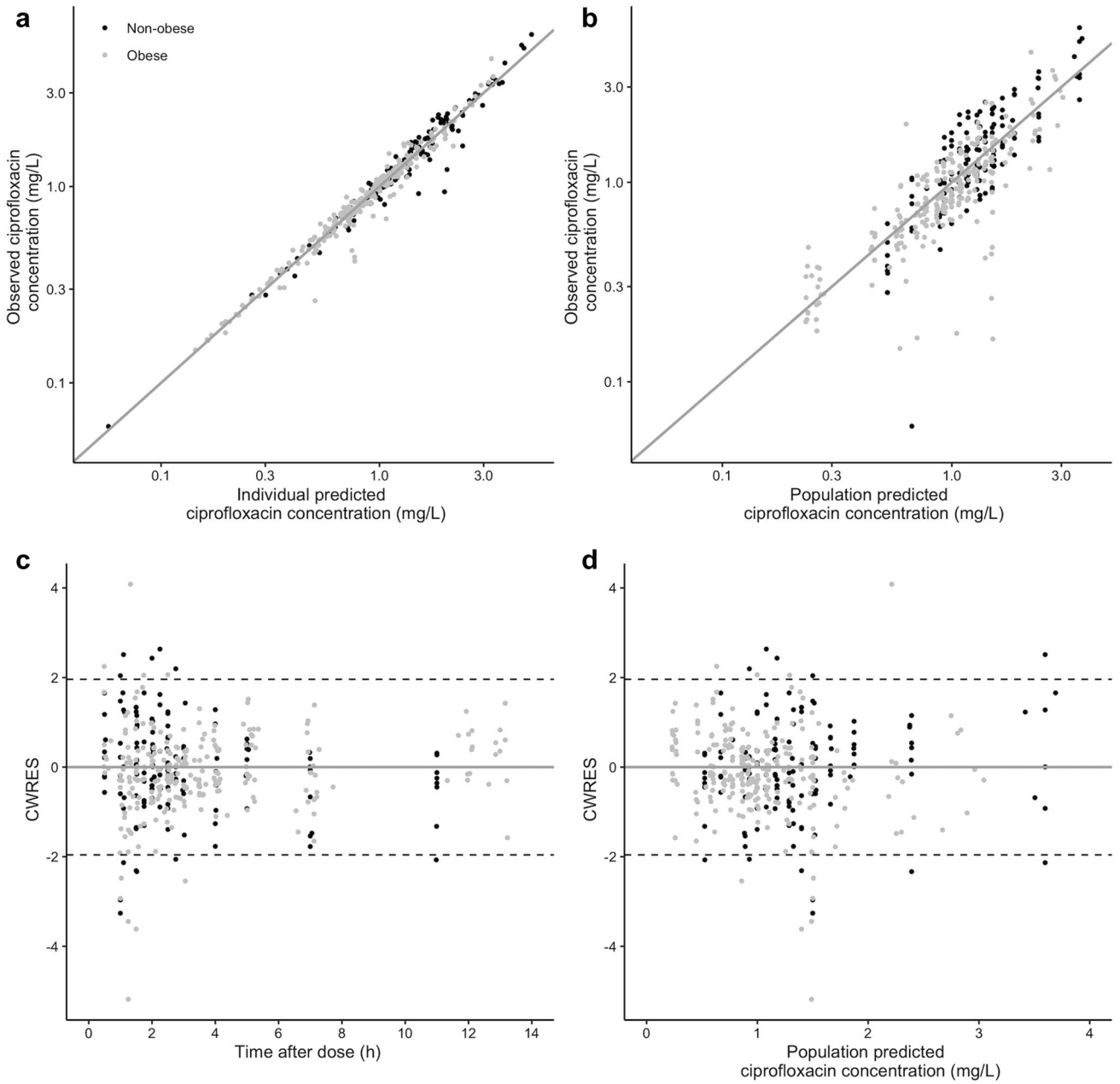

Fig. 1 Diagnostic plots of the final model for morbidly obese individuals (grey dots) and non-obese individuals (black dots). **a** Observed versus individual predicted ciprofloxacin concentrations. **b** Observed versus population predicted ciprofloxacin concentrations. **c** CWRES versus time after dose. **d** Conditional weighted residuals versus population predicted concentration. The grey line represents the line of identity and the dashed lines represent the 1.96, − 1.96 interval indicating the range within which 95% of the observations are expected to fall. *CWRES* conditional weighted residuals

Although ciprofloxacin pharmacokinetics in obese patients has been previously studied, prior studies had shortcomings in their design and showed conflicting results [8, 9]. Hollenstein et al. recruited a cohort of obese participants with a mean ± standard deviation (SD) TBW of 122 ± 22.6 kg and mean ± SD BMI of 41 ± 7.8 kg/m^2, but used a relatively short sampling time of 6 h after infusion, which limits the accurate estimation of clearance, the pharmacokinetic 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 h after infusion, in less severely obese participants with a mean ± SD TBW of 111 ± 22.6 kg. Nevertheless, a 22% increase in volume of distribution, 21% increase in total ciprofloxacin clearance, and 29% increase in renal ciprofloxacin clearance

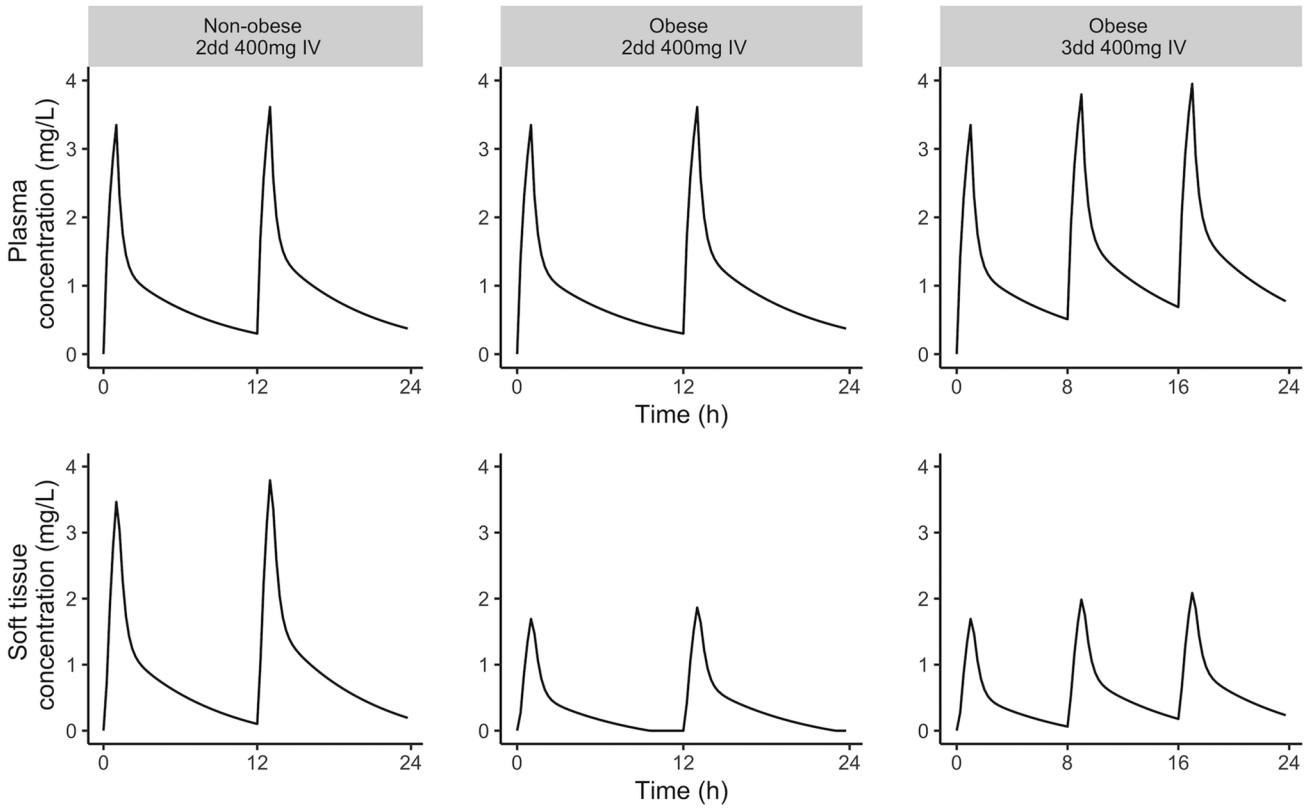

Fig. 2 Concentration-time curves in plasma (top panels) and soft tissue (lower panels) after a two or three times daily IV infusion of 400 mg for a typical non-obese or obese individual based on the empirical extended model derived from data by Hollenstein et al. [8]. *IV* intravenous, *dd* daily doses

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 (57–212 kg), applied a sampling schedule that extends up to 12 h 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 gastrointestinal 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, gastrointestinal mucosa, kidney and epithelial lining fluid was adequate but showed high interindividual variability in the 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 gastrointestinal 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 with 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]. The individual concentration time and demographic data reported by Hollenstein et al. [8] were unavailable and only information from the publication could be used. As such, obesity was modelled 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 reported by Hollenstein et al., exposure in soft tissue would also be similar. This empirical approach does

Table 2 Parameters of the pharmacokinetic model

Parameter	Final model (%RSE)	SIR median [95% CI] 5000 samples/1000 resamples
Fixed effects		
CL (L/h)	31.7 (5.9)	32.1 [29.1–35.0]
V_c (L)	55.4 (16.8)	56.9 [39.9–72.5]
V_p (L)	144 (8.3)	146 [125–166]
Q (L/h)	87.8 (8.1)	89.5 [77.7–101]
F	0.567 (8.9)	0.575 [0.494–0.657]
k_a (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]
Interindividual variability (%)[a,b]		
CL	19.9 (16.6)	20.6 [15.2–25.3]
V_c	76.1 (13.3)	69.8 [51.6–84.7]
V_p	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 the RSE of the estimate

CI confidence interval, *CL* systemic clearance, *F* bioavailability, *ka* absorption rate constant, *MTT* mean transit time, *NN* number of transit compartments, *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; V_c: 10; V_p: 10; Q: 22; F: 28; MTT: 29

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

allow for quantification of ciprofloxacin exposure in soft tissue, but as the applied model structure lacks biological plausibility it does not allow further exploration of underlying biological principles causing the differences in tissue penetration. Based on the available data, potential interindividual differences in tissue penetration ratio and influence from microdialysis techniques could not be studied. With the 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 a TBW of 120–160 kg and four-times-daily regimen for individuals with a TBW > 160 kg. 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.

5 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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-022-01130-5.

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Declarations

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Conflict of interest Roger J.M. Brüggemann declares no conflicts of interest in relation to this current work; however, outside of this work, he has served as a consultant to and received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead Sciences, Merck Sharpe and Dohme Corp., Mundipharma Inc., and Pfizer Inc. All payments were invoiced by the Radboud University Medical Center. Paul D. van der Linden declares membership of the compliance committee of STIZON and is Treasurer of the Dutch Working Party on Antibiotic Policy (SWAB). Koen P. van Rhee, Cornelis Smit, Rene Wiezer, Eric P.A. van Dongen, Roeland E. Wasmann, Elke H.J. Krekels and Catherijne A.J. Knibbe declare no conflicts of interest.

Ethics approval and consent to participate All participants provided written informed consent. The study was registered in the Dutch Trial Registry (NTR6058), approved by the local human research and ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication Not applicable.

Availability of data and material Data are available from the corresponding author upon request.

Code availability Not applicable.

Author contributions Koen P. van Rhee is the lead author and Catherijne A.J. Knibbe is the corresponding author. Writing—original draft: KvR. Writing—review and editing: CK, CS, PvdL, EK, RB, RWa. Conceptualization: CK, CS, EvD, RB, RWi. Investigation: KvR, CS, RWa. Methodology: CK, CS, EK, RB, KvR. Formal analysis: KvR, CS. Project administration: CS, KvR. Supervision: CK, PvdL, RB. Visualization: KvR

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