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

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Part II

Antimicrobial pharmacokinetics in individuals with obesity

CHAPTER 2

2

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

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Abstract

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

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

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

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

Introduction

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

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

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

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

Methods

Study population

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

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

Study design

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

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

Analytical assay

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

Population pharmacokinetic model

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

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

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

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

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

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

Model-based dosing evaluation and optimization

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

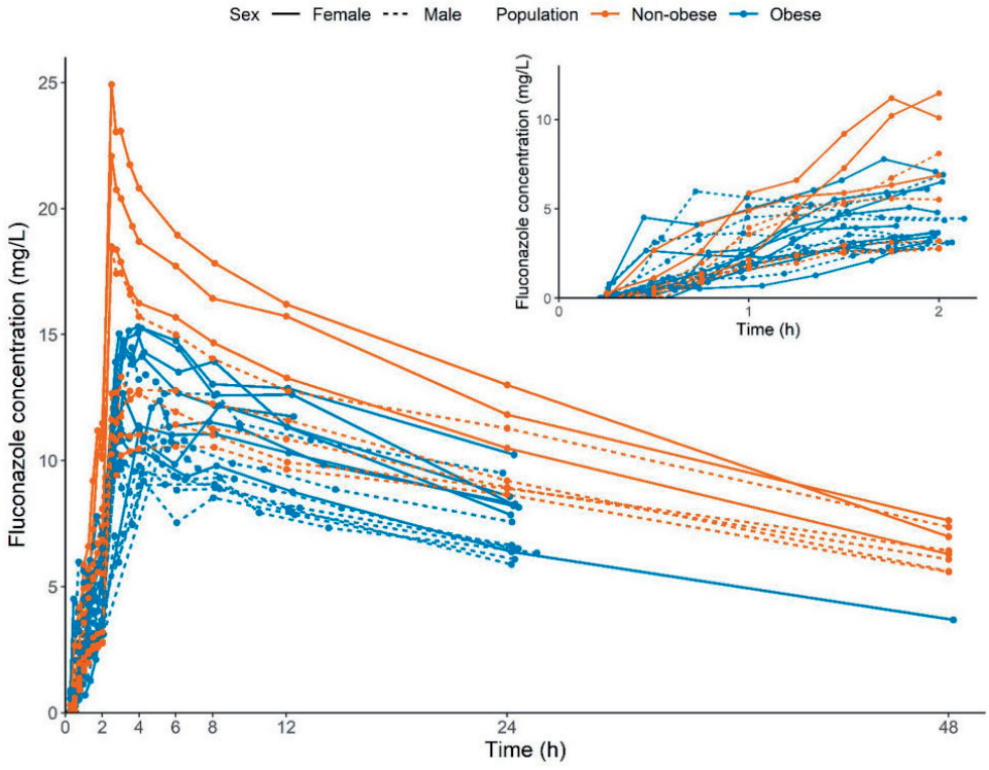
For the treatment of invasive fungal infections, a dose of 800 mg on Day 1 followed by a maintenance dose of 400 mg once daily was evaluated[30]. Other loading (Day 1)/maintenance oral dosing regimens that were evaluated included 400/200 or 200/100 mg, typically used for treating oropharyngeal or esophageal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

Results

Data

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

Figure 1



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

Population pharmacokinetic model

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

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

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

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

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

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

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

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

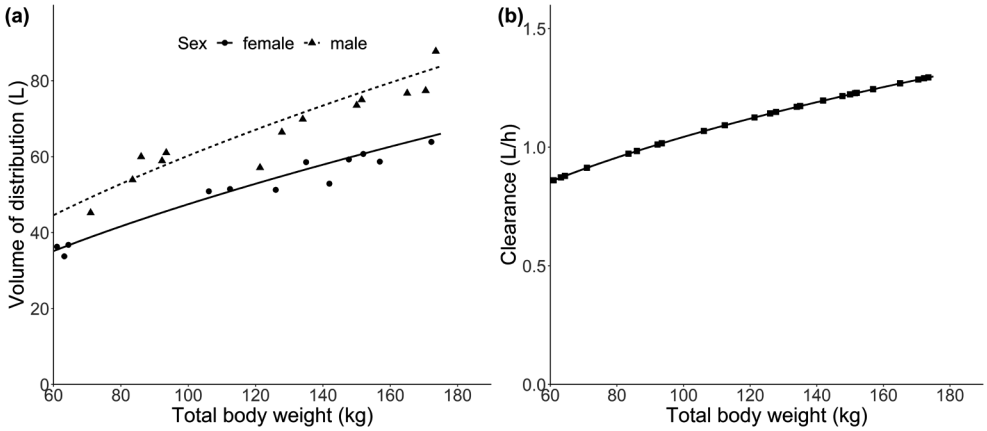
Table 2: Pharmacokinetic parameter estimates for the final model

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

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

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

Figure 2



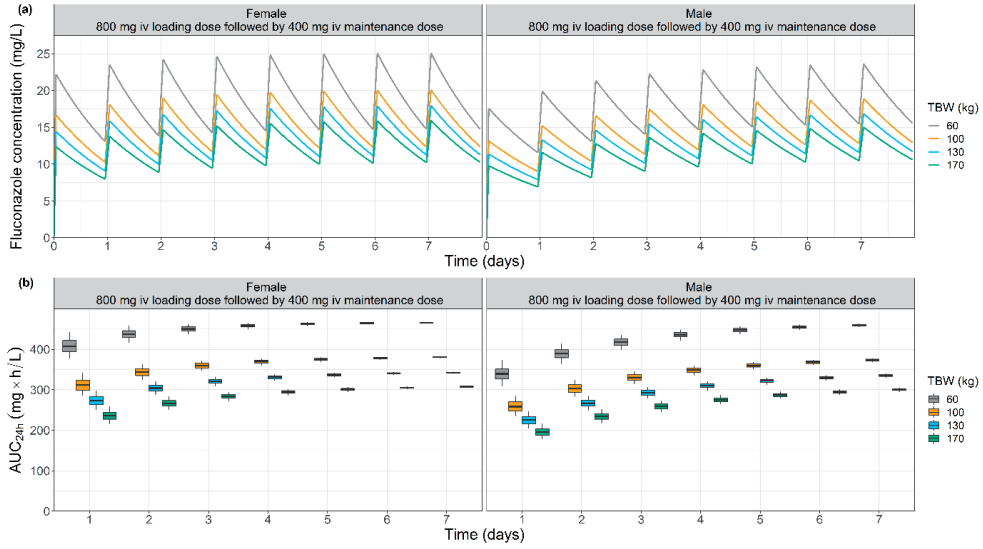
Individual empirical Bayes estimates (filled circles, filled triangles and filled squares) for the Vd (a) and CL (b) versus TBW from the final model. Lines represent the model-predicted relationships between the Vd and CL versus TBW.

Dose evaluations

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

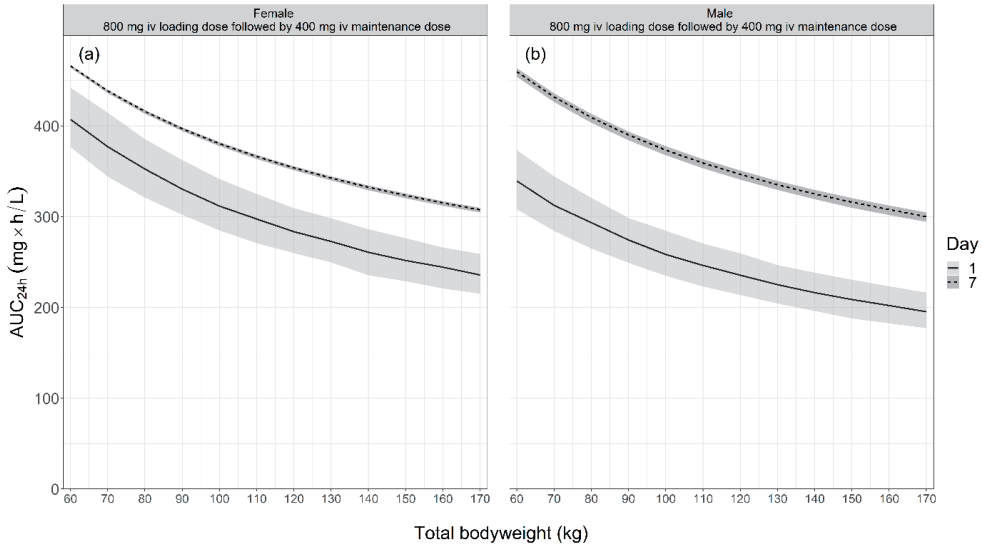
To ensure that all subjects receiving fluconazole IV achieve the target of AUC_{24h}>200 mg*h/L on the first day of treatment, male subjects heavier than 140 kg need a higher loading dose of 600 mg twice daily, compared with 800 mg once daily (Figure 5). To achieve an AUC_{24h}>400 mg*h/L at steady state,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

Figure 3



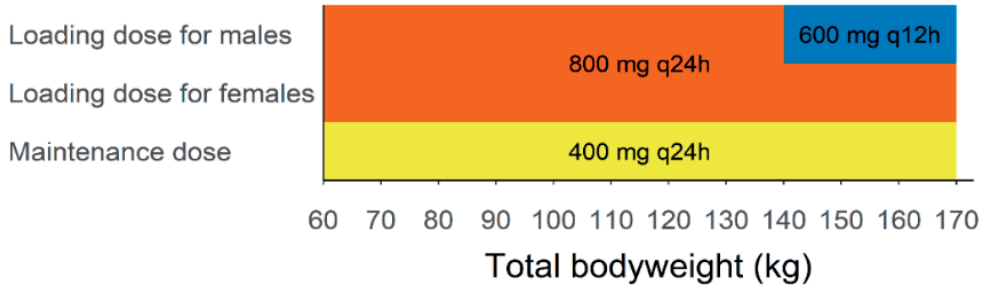
Median fluconazole concentration–time profiles (a) and distribution of the AUC24h (b) based on 1000 simulations of female and male subjects of various TBWs receiving a recommended IV loading dose of 800 mg once daily followed by a maintenance dose of 400 mg once daily. The boxes represent the 25th, 50th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

Figure 4



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

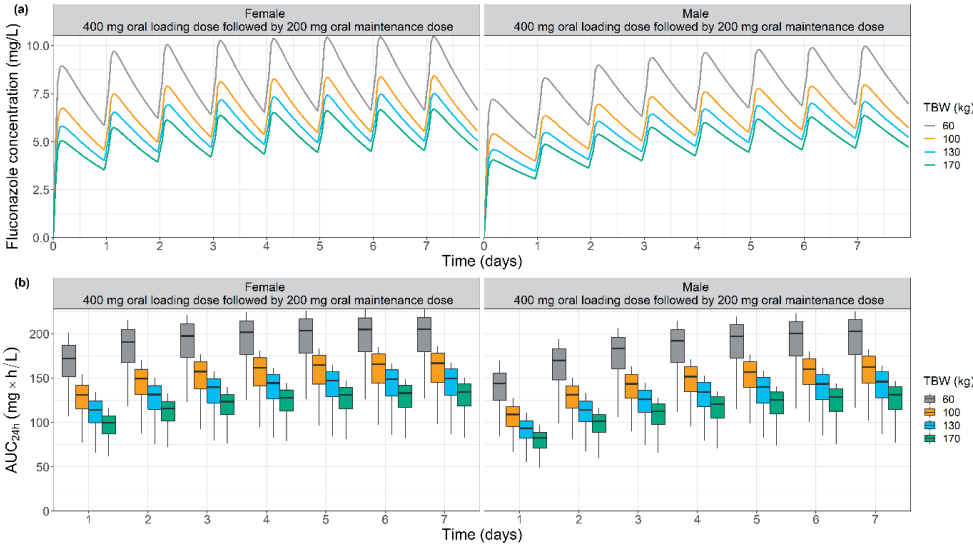
Figure 5



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

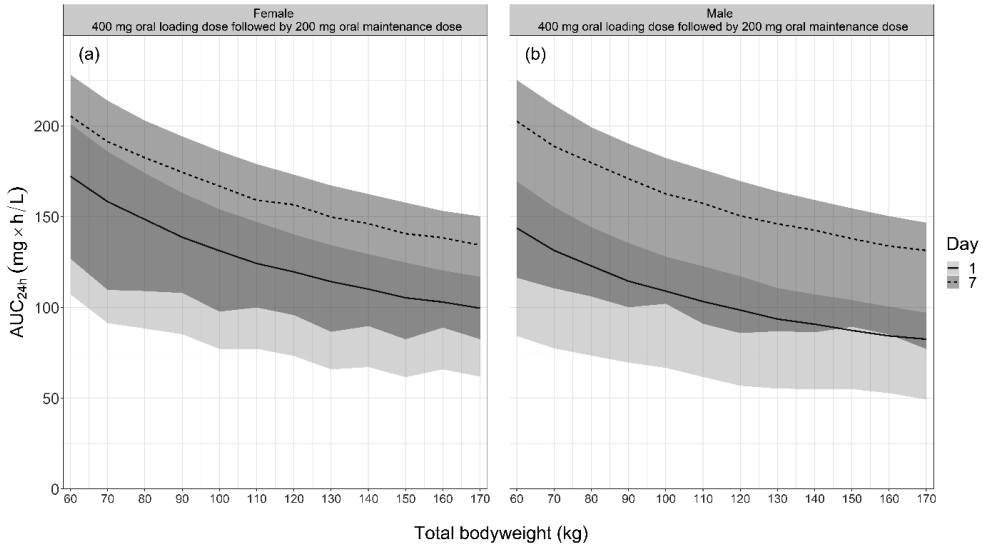
Figures 6 and 7 present simulation results for a commonly used oral dosing regimen prescribed for treating oropharyngeal or esophageal candidiasis. Due to the high IIV on F, exposure is highly variable for all weights. With the lower dose and variable F, no obese individual achieved the target of AUC_{24h}>200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

Figure 6



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

Figure 7



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

Discussion

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

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

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

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

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

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

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

Conclusion

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

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Supplementary material

Table S1: Equations used for calculating body size measures

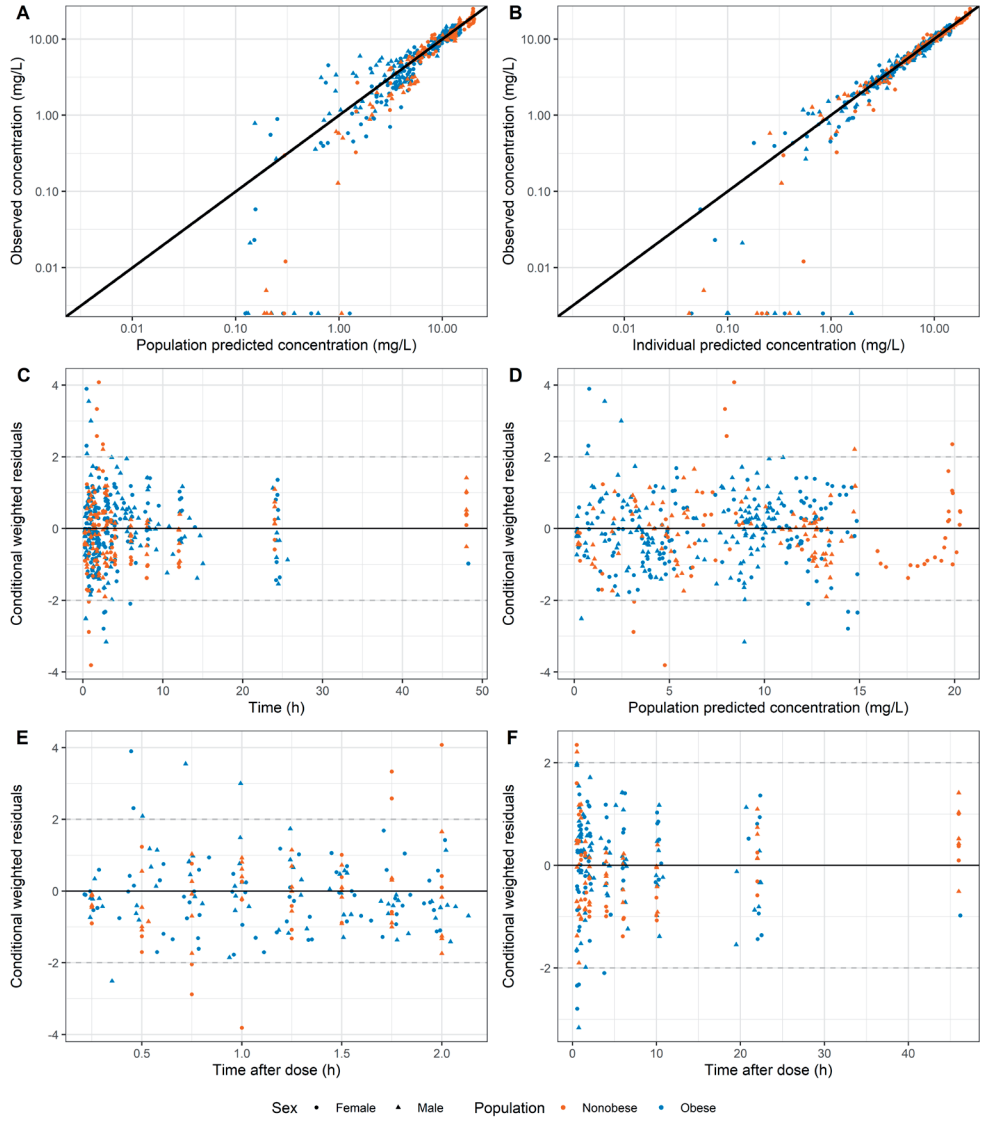
Body size measure	Equation	Reference
Body mass index (BMI), kg/m^2	$BMI = \frac{TBW(kg)}{Height(m)^2}$	
Body surface area (BSA), m^2	$BSA = TBW(kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$	1
Lean bodyweight (LBW), kg	$LBW_{male} = \frac{9270 \times TBW}{6680\ +\ 216\ \times\ \mathrm{BMI}}$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

Table S2: Equations used for calculating renal function indices.

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

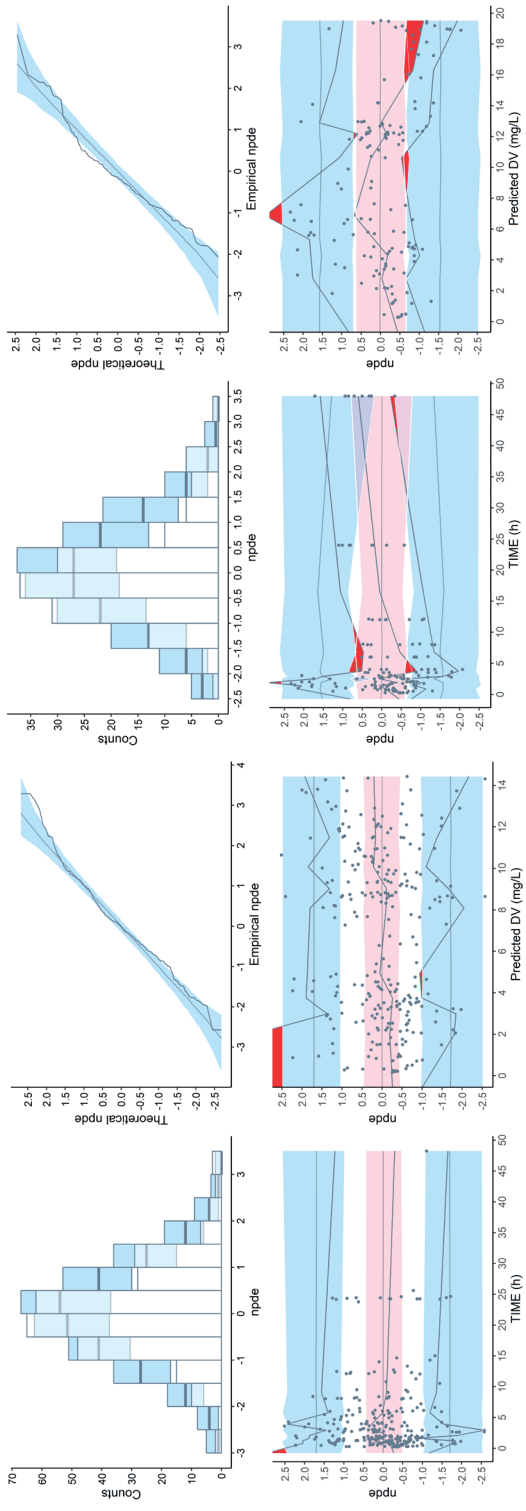
Ucr urine creatinine, Scr serum creatinine

Figure S1



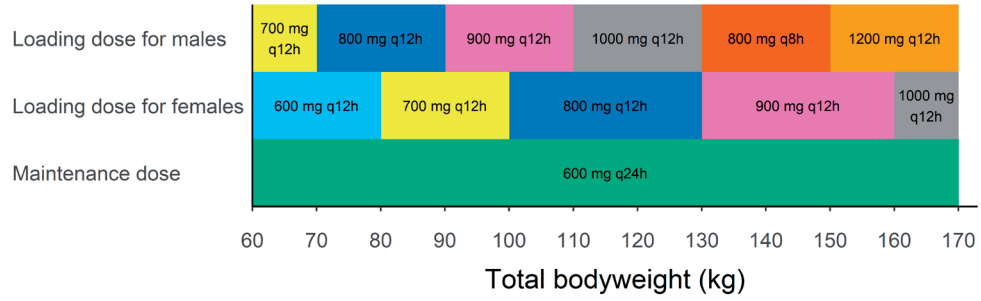
Goodness-of-fit plots of the final population pharmacokinetic model of fluconazole:
a *observed versus population predicted fluconazole concentrations*
b *observed versus individual predicted fluconazole concentrations*
c *conditional weighted residuals versus time after first (oral) fluconazole administration*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

Figure S2



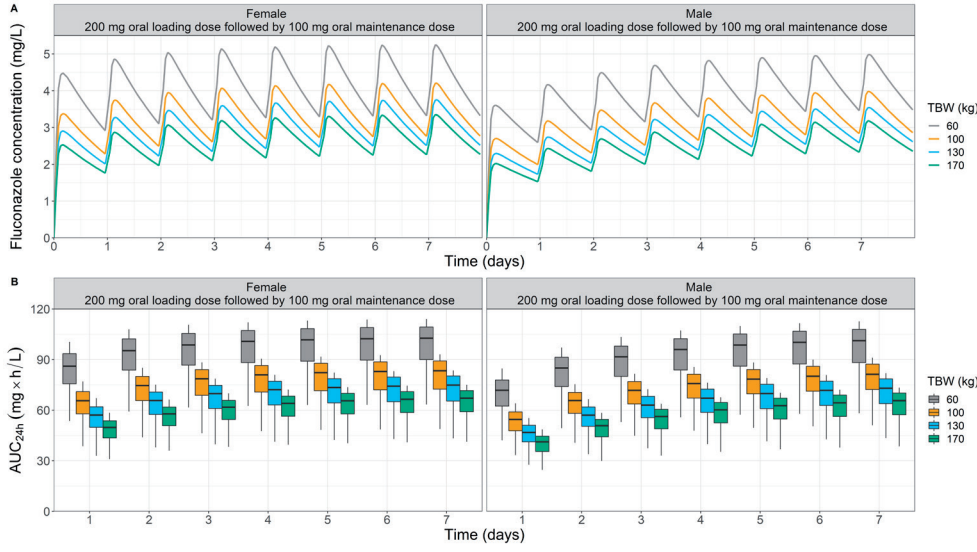
Normalized prediction distribution error (NPDE) results of the final model (n = 1000) stratified for obese (A) and non-obese (B) subjects. In plots of NPDE versus Time and NPDE versus Predicted DV, each prediction interval (95%) is plotted as a colored area (blue for the 2.5 and 97.5th percentiles and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

Figure S3



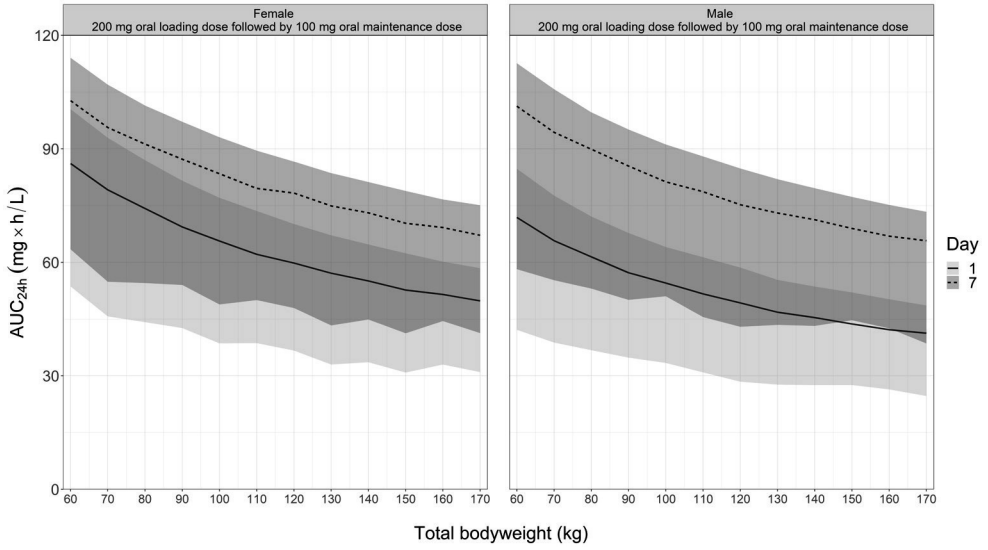
*Simulation-based iv loading dose and maintenance dose of fluconazole for achieving the target of AUC_{24h} > 400 mg*h/L in female and male subjects of various total bodyweight. Target attainment for fluconazole loading dose and maintenance dose was assessed on day 1 and day 7, respectively. A total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

Figure S4



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

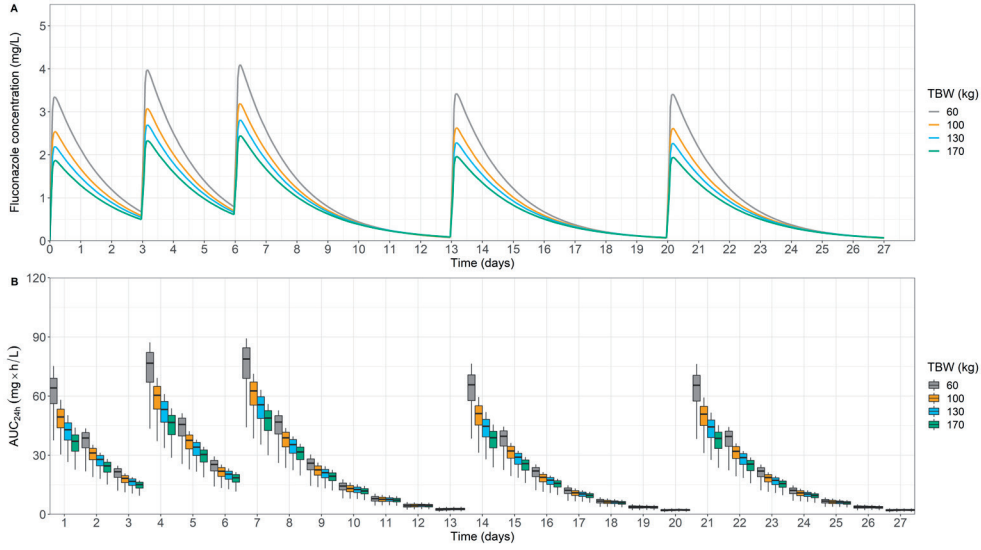
Figure S5



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

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

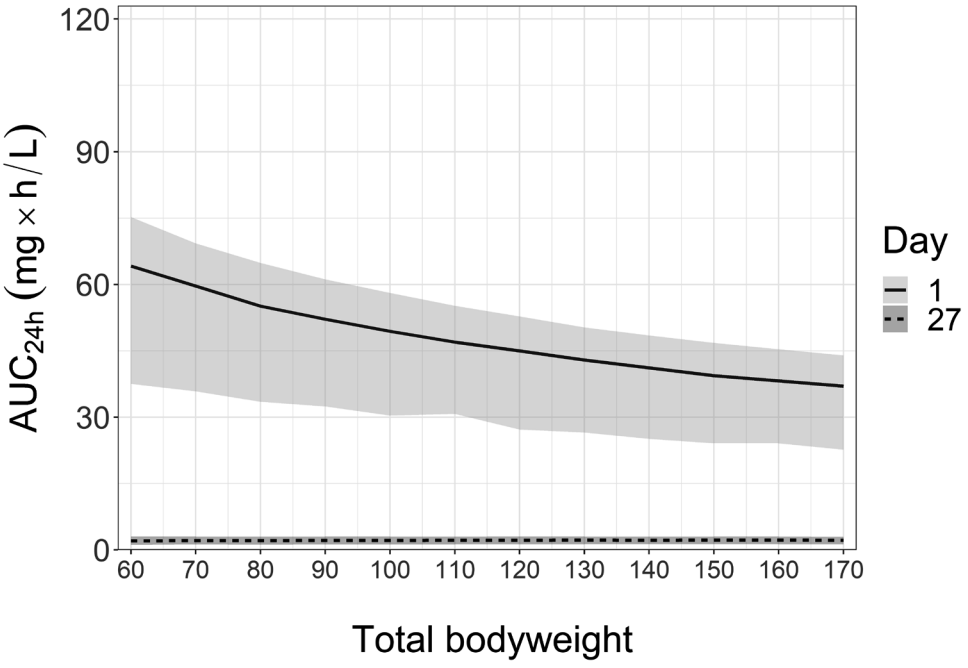
Figure S6



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

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

Figure S7



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

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

NONMEM Control Stream for the Final Model

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

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

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

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

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

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

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

$SIGMA
0.0033 ; Proportional
0.266 ; Additive 0.1 ; Additive

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

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