



Pharmacokinetics of Fluconazole in Obese and Non-obese Adults upon a Semi-simultaneous Oral and IV Study Design

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INTRODUCTION

Obesity is a global pandemic:

- affects the PK of many drugs, may lead to therapeutic failure or toxicity
- limited information on PK changes, dose recommendations are often lacking

Fluconazole is an antifungal drug for preventing and treating candidiasis

METHODS

- **Included patients & study design** (18-65 years, no renal dysfunction, 48% females):
Obese (n=16): BMI ≥ 35 kg/m², scheduled to undergo laparoscopic gastric bypass or sleeve gastrectomy surgery
Non-obese (n=8): $18.5 \leq \text{BMI} < 30$ kg/m²

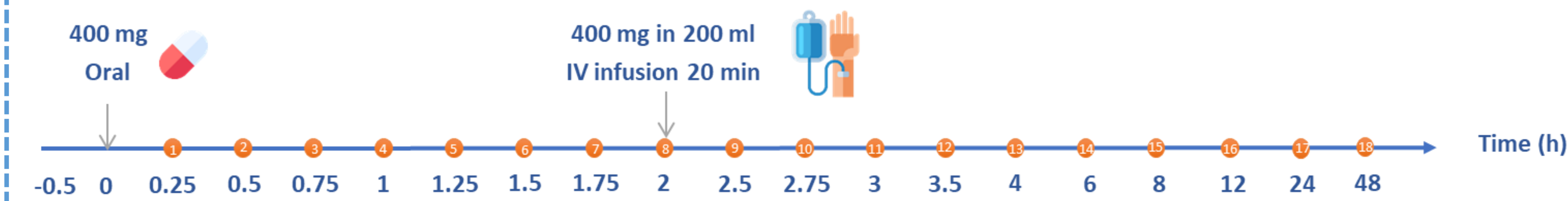


Figure 1 Fluconazole dosing (arrows) and sampling (symbols) schedule.

- **Software:** NONMEM v7.3.0

- **Absorption models tested:**
a. First-order with & without ALAG; b. Transit compartment models^{1,2}; c. Mixed first-order and zero-order³; d. Weibull function²

- **Logit transformation on F**

- **Criteria for model evaluation**

a. OFV; b. Plausibility of parameter values; c. RSE of < 50%; d. Separate goodness-of-fit plots for both oral and IV

- **Simulated dose:** Loading-maintenance 400-200 mg oral

- **Validation:** NPDE, Jackknife

AIM

1. Characterize PK of fluconazole in obese and non-obese upon semi-simultaneous oral and iv dosing;
2. Assess commonly used oral dose.

RESULTS

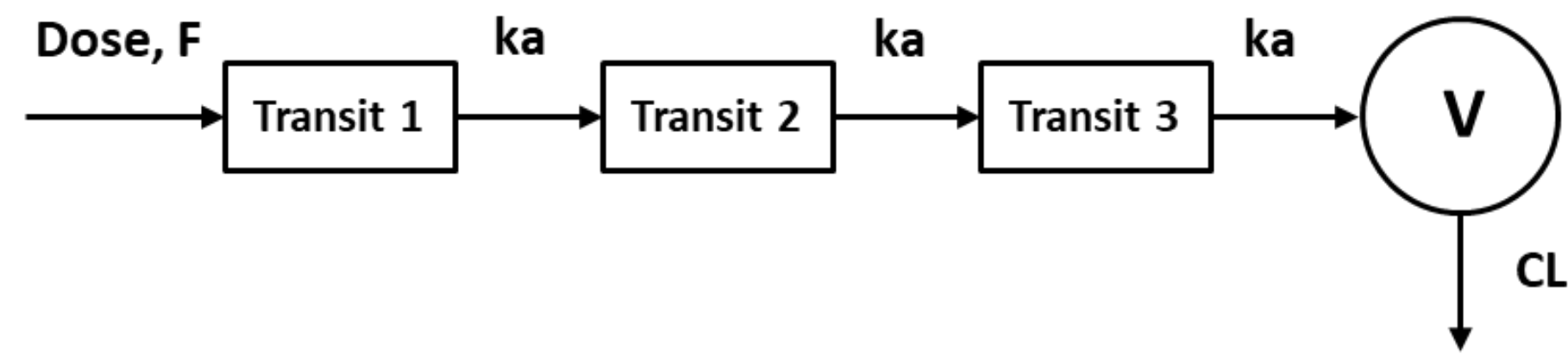


Figure 3 Final structural model.

Table 1 PK parameters estimates of the final model.

Parameters (units)	Estimated value (RSE%)
F (%)	87.5 (7.7)
ka (h ⁻¹)	2.69 (10.5)
CL (L/h)	$CL = CL_{70\text{kg}} \times \left(\frac{TBW}{70}\right)^{\theta_{TBW,CL}}$
CL _{70kg} (L/h)	0.908 (3.0)
$\theta_{TBW,CL}$	0.39 (20.4)
V (L)	$V_{\text{female}} = V_{70\text{kg}} \times \left(\frac{TBW}{70}\right)^{\theta_{TBW,V}}$ $V_{\text{male}} = V_{70\text{kg}} \times \left(\frac{TBW}{70}\right)^{\theta_{TBW,V}} \times (1 + \theta_{\text{sex}})$
V _{70kg} (L)	38.5 (2.5)
$\theta_{TBW,V}$	0.567 (10.6)
θ_{sex}	0.269 (21.0)
Inter-individual variability in variance (RSE%) [shrinkage]	
F	1.25 (51.3) [22.9%]
ka	0.192(14.0) [1.1%]
V	0.0053 (47.5) [24.1%]

F bioavailability, ka absorption rate constant or transfer rate constant, CL clearance, V volume of distribution, TBW total body weight, RSE relative standard error

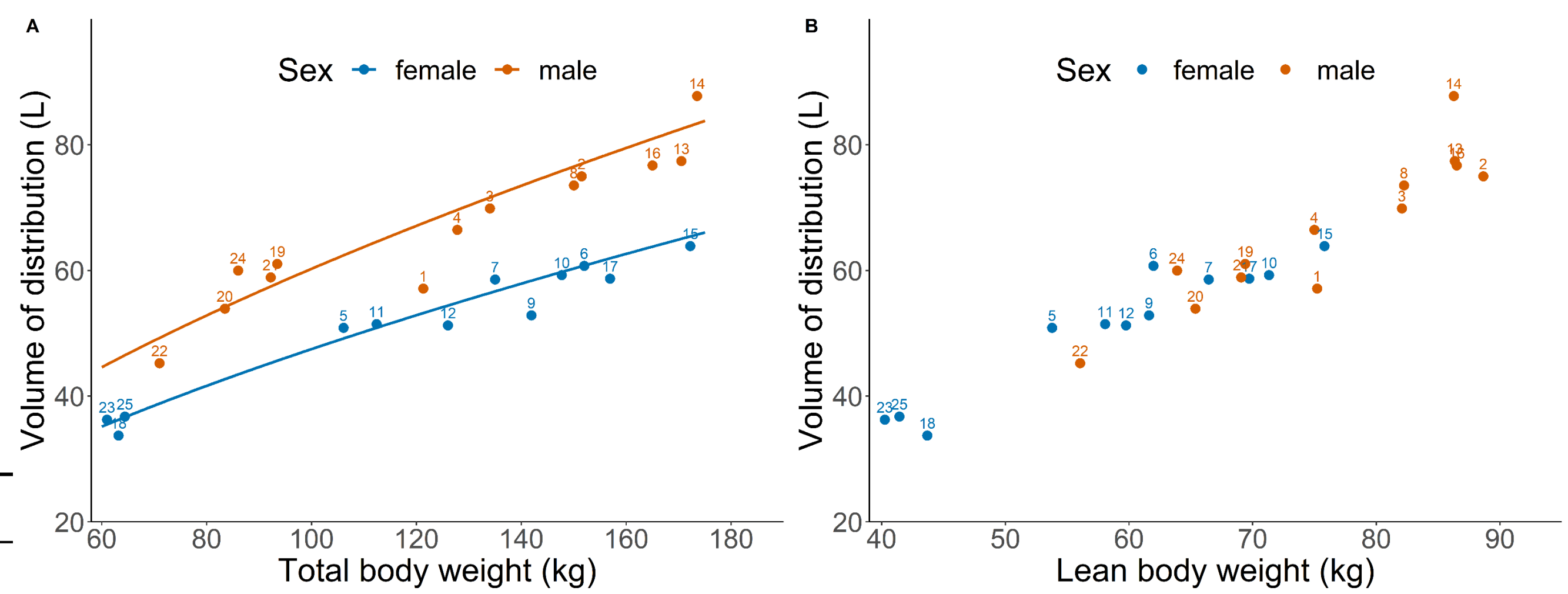


Figure 4 Individual V (symbols) and covariate relationship (lines) versus TBW (A) and versus LBW (B) from the final model.

- ✓ TBW+ sex and LBW showed similar predictive potential for V

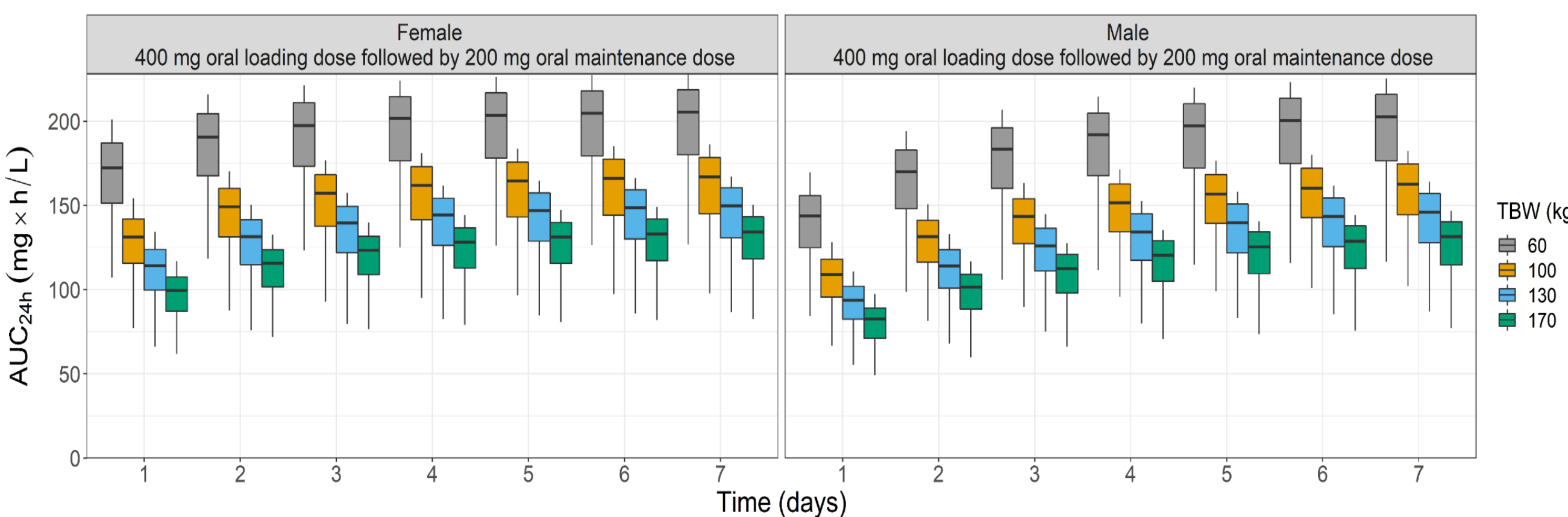


Figure 5 Simulated AUC_{24h} (n=1000) for a common oral loading dose of 400 mg followed by a maintenance dose of 200 mg.

- ✓ $\uparrow \text{TBW} \rightarrow \downarrow \text{AUC}$, AUC: females > males, high variability in AUC

CONCLUSIONS

1. TBW and sex resulted in similar predictive potential on V versus LBW, former was preferred for the ease of clinical application;
2. Both CL and V increase with increasing body weight with sex being an additional covariate for volume resulting in a larger V in males compared to females;
3. Inter-individual variability on F is high (95% distribution interval 43.9-98.4%), high variability in exposure should be anticipated upon oral dosing;
4. Overall, we conclude that severely obese patients are at increased risk of suboptimal exposure upon commonly used dosing regiments.