Bioavailability and the Variability of Posaconazole Exposure in Healthy Volunteers Using a Population Pharmacokinetic Analysis

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INTRODUCTION

- Posaconazole is a triazole antifungal drug and is widely used for prophylaxis and treatment of invasive fungal disease.
- Oral suspension was first marketed and iv was released subsequently, no absolute bioavailability has been reported.
- Suspension showed high inter-individual variability in exposure due to erratic absorption, which can lead to insufficient exposure and result in treatment failure.

AIM

To determine for the first time the absolute oral bioavailability of posaconazole suspension and quantify inter-individual variability of posaconazole pharmacokinetics in healthy volunteers.

METHODS

Two healthy volunteer studies of oral suspension[1] and iv administration were conducted at Radboud University Medical Center (Table 1).

Table 1 Posaconazole PK data and participant demographics.

Parameter	Oral suspension	IV
No. of subjects	20	8
Dosage regimen	400 mg BID	300 mg
Sampling timepoints	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h after dose at day10	0.75, 1, 1.25, 1.5, 2, 4, 8, 12, 24, 48h after infusion
Sex (M/F)	11/9	4/4
Median age (range) in yrs	37.5 (18-54)	22 (20-37)
Median weight (range) in kg	74.0 (44-104)	72.3 (61.4-85.4)
Median BMI (range)	23.1 (18.3-29.4)	22.5 (20.2-25.4)

Population pharmacokinetic models were established using NONMEM v7.3. Three models were tested for fitting the 2nd peak observed in oral dose (Figure 1). One and two compartment were tested for structure model. Age and weight were tested as covariates.

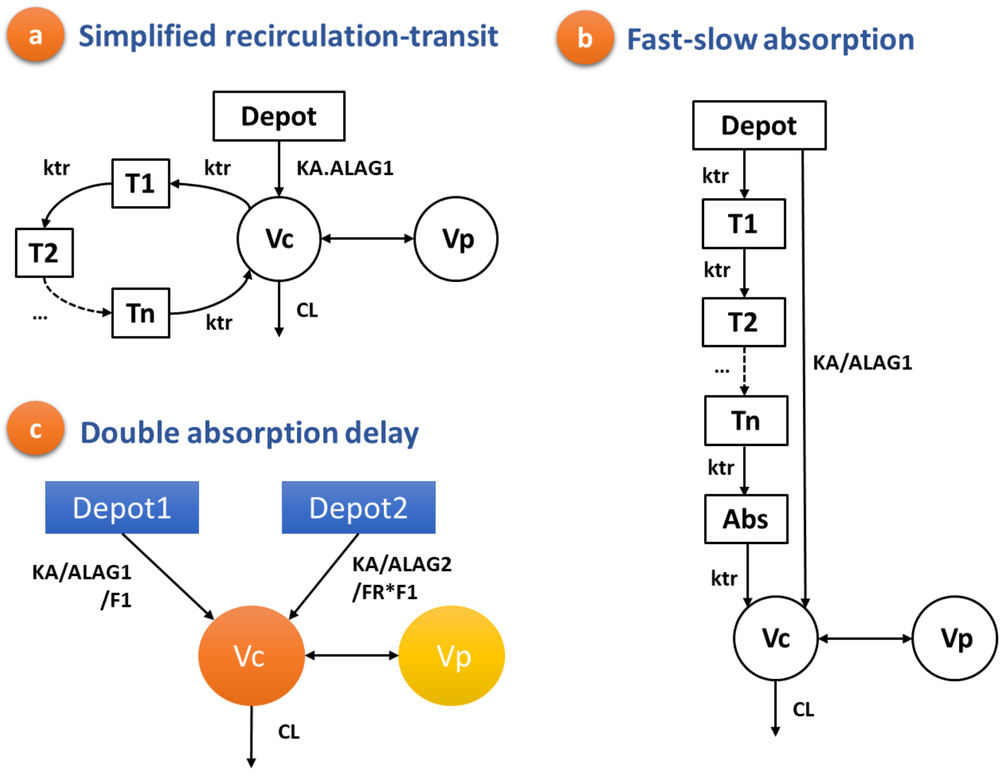

Figure 1 Models tested for fitting the second peak.

RESULTS

- Extra depot to quantify the recirculation fraction from the 2nd peak of the oral suspension (Figure 1c)
- First-order absorption and elimination, proportional error
- Absolute bioavailability: 55.2%
- Recirculation fraction: 19.2%
- No statistically significant covariate
- AUC_{24} is 3.7% lower with the consideration of the 2nd peak

Table 2 Parameter estimates.

Parameter	Value (RSE%)		IIV(%) (RSE%)	
	No 2nd peak	2nd peak	No 2nd peak	2nd peak
CL	5.8 (8.0)	6.8 (12.1)	27.7 (26.5)	31.5 (25.7)
Vc	170.0 (15.4)	164.0 (13.3)	22.3 (14)	22.8 (13.9)
F1	45.1% (9.7)	46.3% (12.0)	25.2 (27.4)	20.9 (42.2)
Q	32.9 (55.9)	29.1 (62.5)		
Vp	86.7 (30.8)	84.0 (31.4)		
KA	0.9 (18.2)	0.8 (17.6)		
ALAG1	1.8 (3.3)	1.8 (3.3)		
ALAG2		8.8 (8.1)		
FR		19.2% (38.6)		

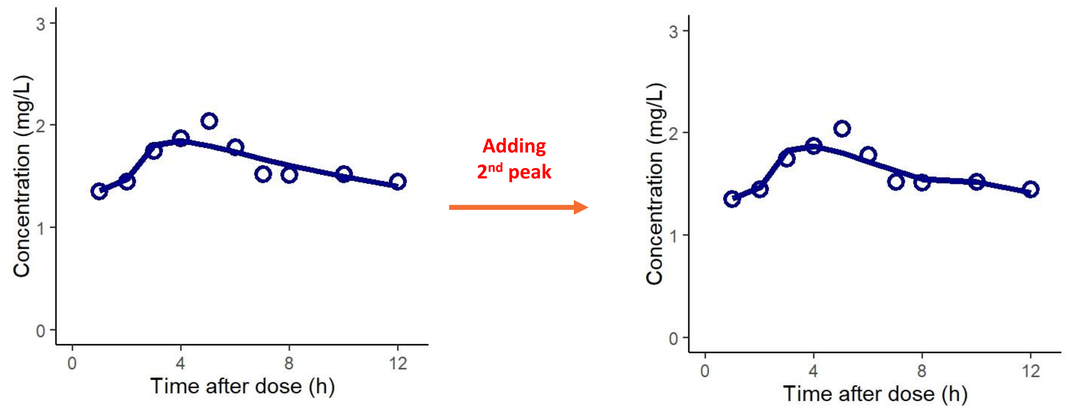

Figure 3 IPRED change with 2nd peak consideration

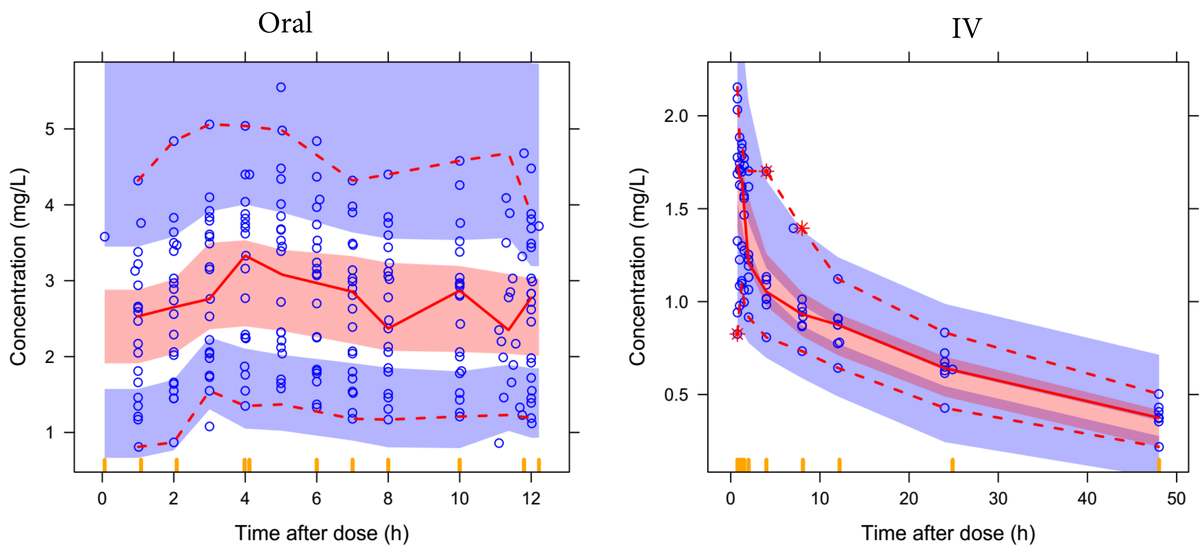

Figure 4 Visual predictive check of final model.

CONCLUSIONS AND PERSPECTIVES

- The absolute oral F of posaconazole suspension is 55.2%.
- The absolute oral F and the variability of the posaconazole suspension in various patient populations is part of further investigation.

[1]Bruggemann R. J., et al. J Antimicr Chemother, 2010, 65 (10): 2188-94.