

# Population Pharmacokinetic-Pharmacodynamic Modeling of Escitalopram in Patients with Obsessive-Compulsive Disorder Using Yale-Brown Obsessive Compulsive Scale

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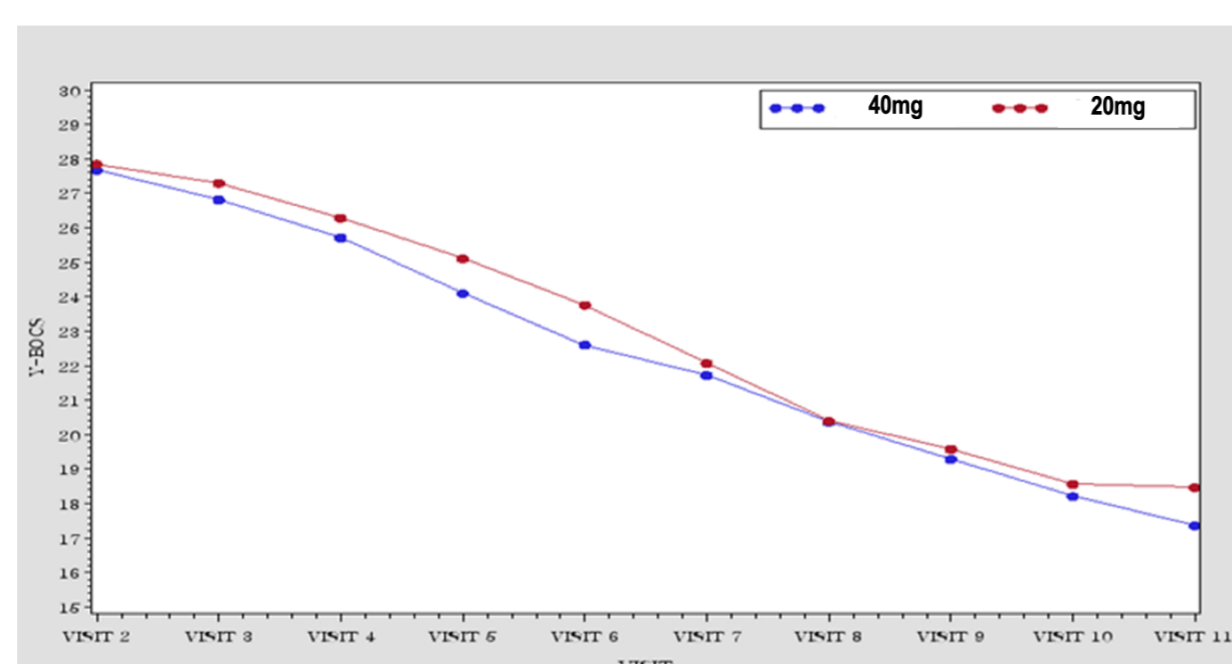
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## INTRODUCTION

- Obsessive compulsive disorder (OCD) is a clinically heterogeneous syndrome characterized by intrusive obsessions and highly repetitive and ritualized compulsions
- Serotonergic system including serotonin transporter(SERT) has attracted considerable attention in relation to the pathophysiology of OCD, initially supported by the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs)
- Reduced availability of SERT in drug-naïve or -free OCD has been shown, however treatment effect with SSRI on the availability of the SERT were not observed
- Escitalopram is one of SSRIs proven to be effective in treating OCD and its conventional dose approved for OCD is ~ 20mg/day
- However, clinical experience is indicating higher dose than the conventional dose might be effective for OCD
- In contrary to clinical experience, the effect of high dose(40mg) escitalopram on clinical improvement in patients with OCD was not proven in prior randomized clinical trial



- The conventional approach comparing two groups as above could have limited the statistical power to detect the dose-response relationship.
- Thus, we re-analyzed the data using pharmacokinetic-pharmacodynamic modeling

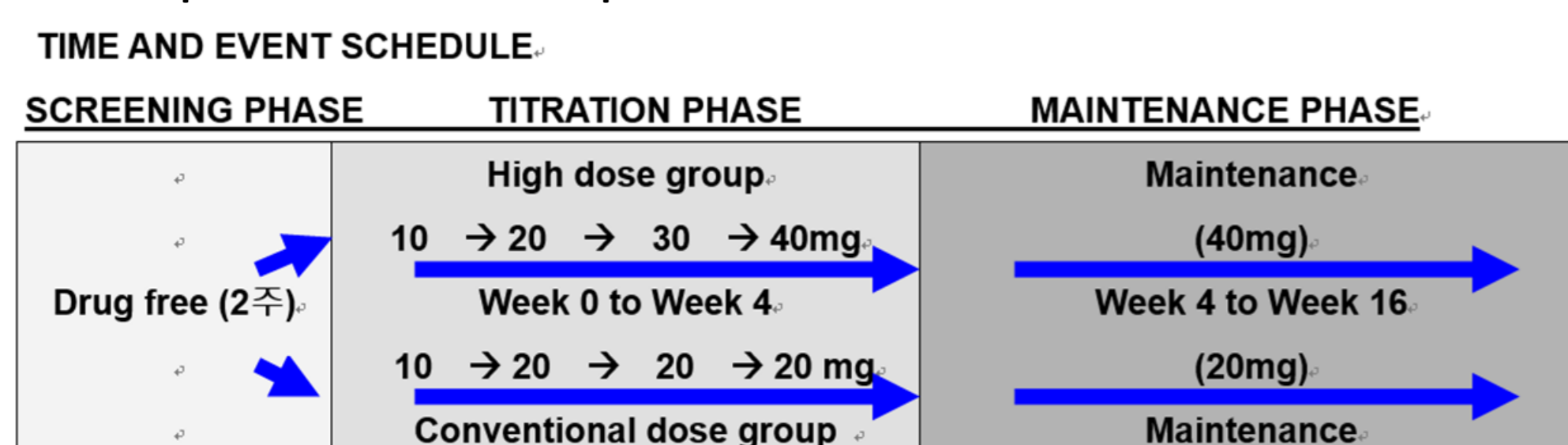
## OBJECTIVE

- To develop pharmacokinetic-pharmacodynamic (PK-PD) model of escitalopram and its therapeutic effect on obsessive-compulsive symptom
- To evaluate dose-effect relationship of escitalopram in OCD with developed PK-PD model

## METHODS

### Data for Pharmacokinetic-Pharmacodynamic (PK-PD) model

- Data from 91 OCD patients enrolled in prior study
  - Randomized, double-blind, multi-center design
  - Steady-state plasma escitalopram concentrations and YBOCS scores



- Data from 12 male healthy volunteers
  - single-blind, single oral parallel dose group design
  - 5, 10, 20 and 30mg of escitalopram
  - escitalopram plasma concentrations at 1, 2, 3,4,5, 6, 8, 10, 22, 24, 46 and 72 h after the administration of escitalopram

### Population Model Building

- PK and PK-PD models were built with population nonlinear mixed effects modeling using NONMEM version 7.3.0 software (GloboMax, Ellicott City, MD, USA)
- Nonlinear mixed effects modeling simultaneously estimates fixed effects and random effects in the models
- The fixed effects are the pharmacological parameters in the models (clearance, volume of distribution, Imax and IC50).
- The random effects model inter-individual variability and residual variability

### PK-PD Modeling

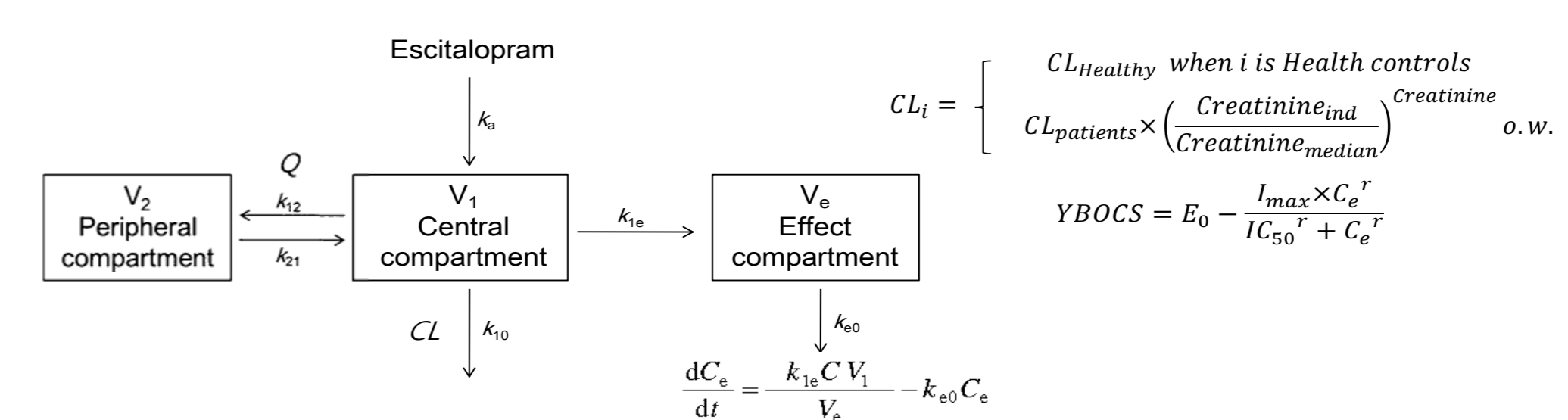
- A sequential modeling approach was used for the PK-PD modeling. Population PK analysis was performed, and the individual PK parameter estimates were used in the population PD analysis

## RESULTS

Table 1. Demographic characteristics and clinical data

mean±SD	Patients			Healthy controls
	High dose (40mg)	Low dose (20mg)	Total	
N	45	46	91	12
Age (yr)	30.9±14.4	30.1±12.7	30.5±13.5	23.0±2.7
Sex (M/F) (ratio)	34(75.6%)/11(24.4%)	32(69.6%)/14(30.4%)	66(72.5%)/25(27.5%)	12(100%)/0(0%)
Height (cm)	170.6±9.2	169.5±7.7	170.0±8.4	173.1±7.0
Weight (kg)	67.7±15.3	63.4±12.0	65.5±13.8	68.7±7.5
Creatinine	0.891±0.156	0.890±0.163	0.891±0.159	-
Baseline YBOCS	27.4±4.9	27.6±4.6	27.5±4.7	-

Table 2. PK-PD model and its parameter estimates

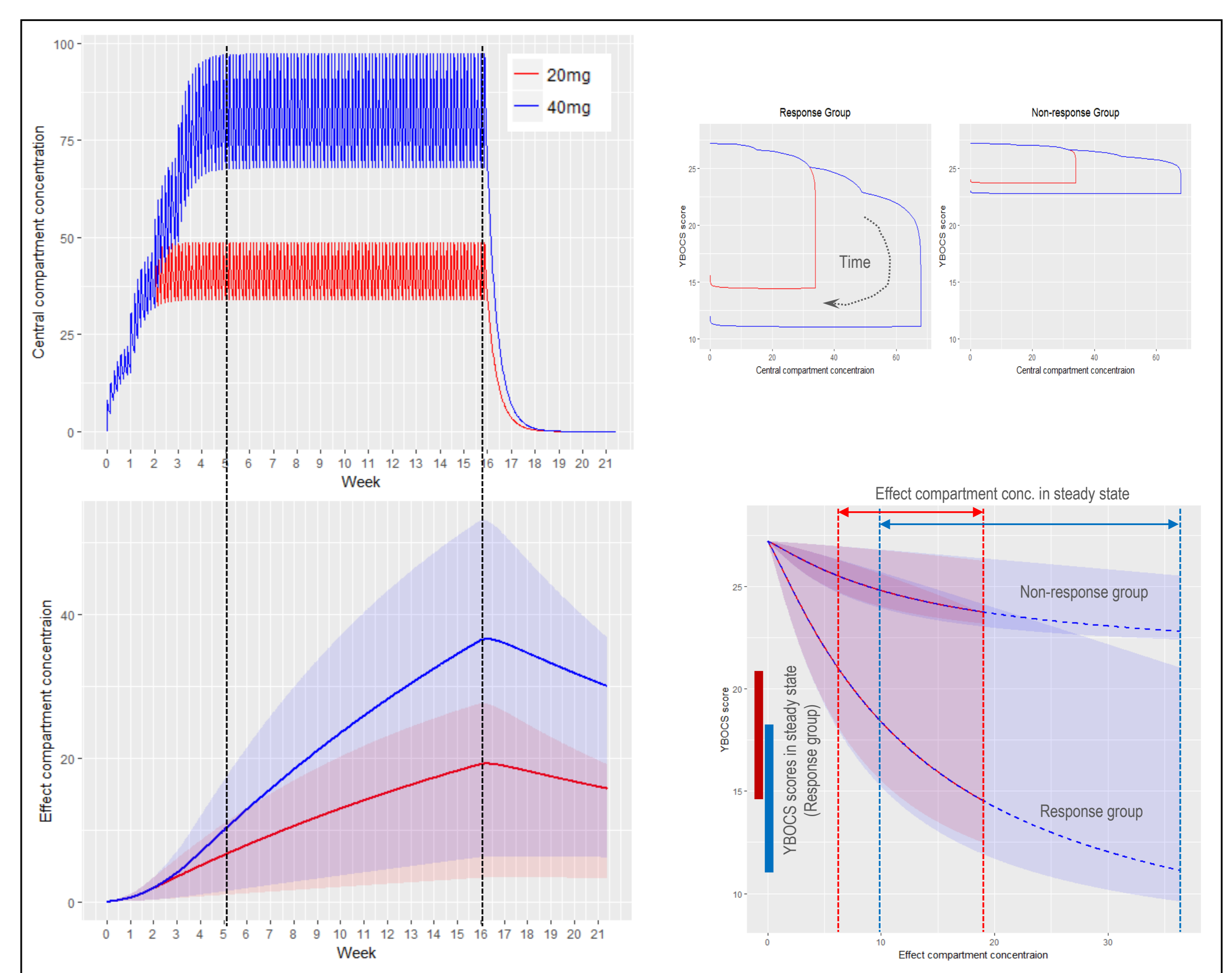


Model	Parameter	Estimate	SE	RSE(%)	95% CI	Inter-individual variability(%)
2 Compartment PK model (OFV : 1335.959)	CL(Healthy)	35.1	-	-	30.67- 46.51*	36.02
	CL(Patients)	20.5	-	-	16.88 - 21.04*	37.41
	Creatinine	0.64	-	-	NA	13.09
	Vd	835	-	-	326.62 - 1269.28*	-
	Ka	0.725**	-	-	NA	-
	Q	126**	-	-	NA	-
	Vp	644**	-	-	NA	-
Inhibitory Sigmoid Emax PD model (OFV : 2673.753)	E0	27.2	0.49	1.79	26.25 - 28.15	16.88
	Imax(resp)	0.784	0.101	12.88	0.59 - 0.98	16.85
	Imax(non)	0.214	0.0423	19.77	0.13 - 0.30	73.40
	IC50	13.6	3.92	28.82	5.92 - 21.28	0.003
	GAM	1.14	0.168	14.74	0.81 - 1.47	60.17
	Ke0	0.000251	0.000111	44.22	0.00003344 - 0.00046856	94.98

\* : bootstrap results

\*\* : values fixed as parameter estimates from healthy control

Figure 1. Simulated result based on PK-PD model



## DISCUSSION

- Developed model describes the relationship between dose of escitalopram and its therapeutic response based on improvements of YBOCS scores adequately
- PK-PD model might show additional treatment effect of high dose escitalopram compared with conventional dose on clinical improvement in patients with OCD