

A (semi)physiologically based pharmacokinetic (semi-PBPK) model incorporating genetic polymorphism of CYP2D6 to predict the nonlinear kinetics of paroxetine

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Background & objectives

Background: Paroxetine exposure increases more than linear with increasing doses and with decreasing number of active CYP2D6 alleles, which precludes individualized dosing by simple methods.¹

Objective: The aim of this study was to develop a population pharmacokinetic model for paroxetine in order to describe its nonlinear kinetics among different genotypes.

Methods

Data source: Pharmacokinetic profiles of paroxetine after single oral dose of 20 mg in 40 healthy subjects were obtained from a previous 2-period bioequivalence study. CYP2D6 genotyping were conducted in all subjects.

Analysis tool: Data were analyzed using nonlinear mixed-effects modeling implemented in NONMEM V7.3.0.

Intermediate results: Please see table 1.

Tab.1. Pharmacokinetic models developed in the study

	Models	Assessment
1	Conventional two-compartment PK model with Michaelis-Menten kinetics	Estimation for population predicted concentration more than 5 ng/ml is not available
2	One-compartment semi-PBPK model with additional liver and enzyme compartments	CYP2D6 clearance for allele variant s*9, *41 is not reasonable
3	Two-compartment semi-PBPK model with additional liver and portal vein compartments	The goodness fit plots are the best at present. but can't explain nonlinear kinetics
4	Two-compartment semi-PBPK model with additional liver, portal vein and enzyme compartments	The objective function value is much lower than other models. It can explain nonlinear kinetics process well by incorporating enzyme autoinhibition.

We used model 4 as our present final model. The process can be described as follows:

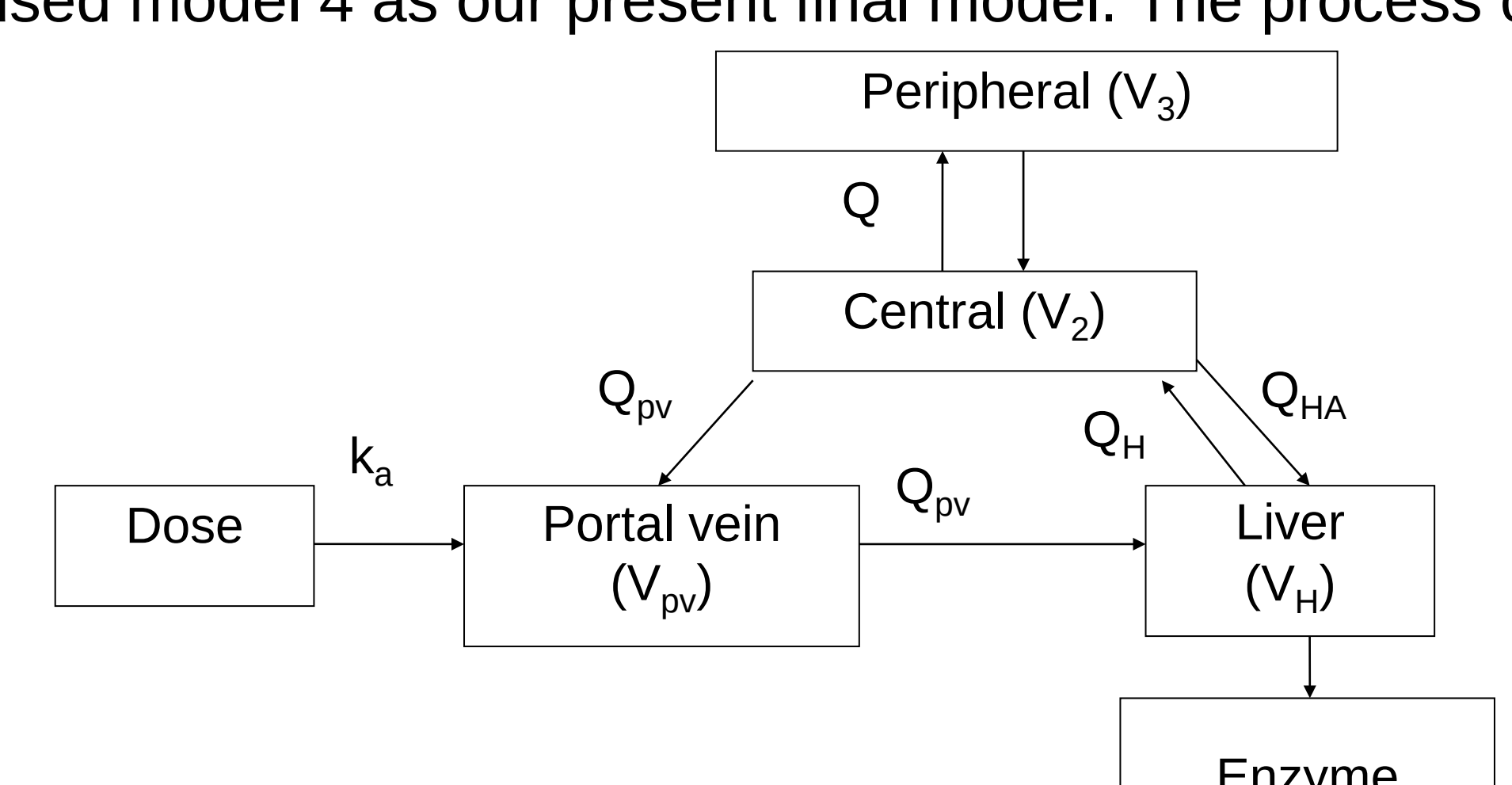


Fig. 1. Semi-PBPK model for the description of Paroxetine

Based on the model, the mass-balance equations are expressed as eqs.1 to 6.

$$\frac{dA_1}{dt} = -k_a \cdot A_1 \tag{1}$$
$$\frac{dA_2}{dt} = Q_H \cdot \frac{A_4 \cdot R_B}{V_H \cdot K_P} - \frac{Q_{HA} \cdot A_2}{V_2} - \frac{Q_{PV} \cdot A_2}{V_2} - \frac{Q \cdot A_2}{V_2} + \frac{Q \cdot A_3}{V_3} \tag{2}$$
$$\frac{dA_3}{dt} = \frac{Q \cdot A_2}{V_2} - \frac{Q \cdot A_3}{V_3} \tag{3}$$
$$\frac{dA_4}{dt} = \frac{Q_{PV} \cdot A_5}{V_{PV}} - fu_p \cdot CL_{INT} \cdot \frac{A_4}{V_H \cdot K_P} - Q_H \cdot \frac{A_4 \cdot R_B}{V_H \cdot K_P} + \frac{Q_{HA} \cdot A_2}{V_2} \tag{4}$$
$$\frac{dA_5}{dt} = k_a \cdot A_1 - \frac{Q_{PV} \cdot A_5}{V_{PV}} + \frac{Q_{PV} \cdot A_2}{V_2} \tag{5}$$
$$\frac{dE_t}{dt} = R_0 - k_{DEG} \cdot E_t - \frac{k_{INACT} \cdot fu_p \cdot \frac{A_3}{V_H \cdot K_P}}{K_{APP} + fu_p \cdot \frac{A_3}{V_H \cdot K_P}} \cdot E_t \tag{6}^{2,3}$$

$$R_0 = k_{DEG} \cdot E_0$$
$$CL_{INT} = CL_B + CL_{CYP2D6} \cdot E_t / E_0$$
$$CL_{CYP2D6} = \sum_i^m n_i \cdot CL_{EXT} + \sum_i^m n_i \cdot CL_{POOR}$$

k_a = absorption rate constant; Q_{PV}^* = hepatic portal blood flow; Q_{HA}^* = hepatic arterial blood flow; Q_H^* = hepatic blood flow; V_{PV}^* , V_H^* , V_2 , V_3 = volumes of portal vein, liver, central and peripheral compartments; Q , CL_{INT} , CL_B and CL_{CYP2D6} = intercompartmental, intrinsic, basal and enzyme clearance. i =index for CYP2D6 expressing variants(e.g. $i=1$ for *1) and n_i is the number of copies of the respective allele; fu_p^* = fraction unbound in plasma; K_p^* = liver/blood partitioning coefficient; R_B^* =blood/plasma partitioning coefficient; E_t = amount of active CYP2D6 enzymes; R_0 = zero order rate of CYP2D6 enzyme synthesis; E_0^* =amount of active CYP2D6 enzymes at t=0 (set to 100%); k_{DEG}^* = first-order turnover rate constants of CYP2D6 enzymes; k_{INACT}^* = maximum rate of inactivation; K_{APP} = concentration of mechanism-based inhibitor associated with half maximal inactivation rate.
* values fixed based on literature

Results

A two-compartment semi-PBPK model with additional compartments for liver, portal vein and enzyme was developed. Different CYP2D6 allele variants clearance are estimated by grouping them into extensive and poor clearance according to their similar activity. Among the covariate relationships tested, weight was identified as a significant covariate on volume of distribution of the central compartment. Currently, the model can preliminarily describe the nonlinearity of the kinetic process. The final estimations for the present model are shown as **Table 2**.

Tab. 2. Pharmacokinetic parameters of the current model

Parameter (unit)	Definition	Estimate (RSE)
θ Estimates		
CL _B (l/h)	Basal Clearance	1270 (21%)
CL _{EXT} (l/h) ⁴	CYP2D6 clearance per allele variant *1, *2 or *35	10400 (20%)
CL _{POOR} (l/h) ⁴	CYP2D6 clearance per allele variant *9, *41	6260 (61%)
Q (l/h)	intercompartmental clearance	42.8 (36%)
V _{PV} (l)	Volume of portal vein	22.2 (22%)
V ₂ (l)	Volume of distribution in central compartment	379 (12%)
V ₃ (l)	Volume of distribution in peripheral compartment	282 (25%)
K _{APP} (ng/ml)	inhibitor concentration when providing half-maximal inactivation rate of CYP2D6	1.95 (41%)
k _a (h ⁻¹)	Absorption rate constant	0.584 (20%)
WGT on V ₂	Weight effect on V ₂	1.35 (34%)
ω ² Estimates		
IIV CL _B (CV%)	Inter-individual variability on basal clearance	83.2% (15%)
IIV CL _{CYP2D6} (CV%)	Inter-individual variability on total CYP2D6 clearance	79.8% (15%)
IOV CL _{CYP2D6} (CV%)	Inter-occasional variability on total CYP2D6 clearance	33.9% (25%)
IIV V _{PV} (CV%)	Inter-individual variability on portal vein volume	153.4% (15%)
IIV V ₂ (CV%)	Inter-individual variability on central volume of distribution	35.2% (21%)
IIV V ₃ (CV%)	Inter-individual variability on intercompartmental clearance volume of distribution	22.1% (22%)
IIV k _a (CV%)	Inter-individual variability on absorption rate constant	37.6% (27%)
σ ² Estimates		
Proportional Error (CV%)		0.0239 (8%)

RSE relative standard error (provided by NONMEM); **CV** coefficient of variation; **CV%** for IIV and IOV computed as sqrt(exp(ω²)-1).

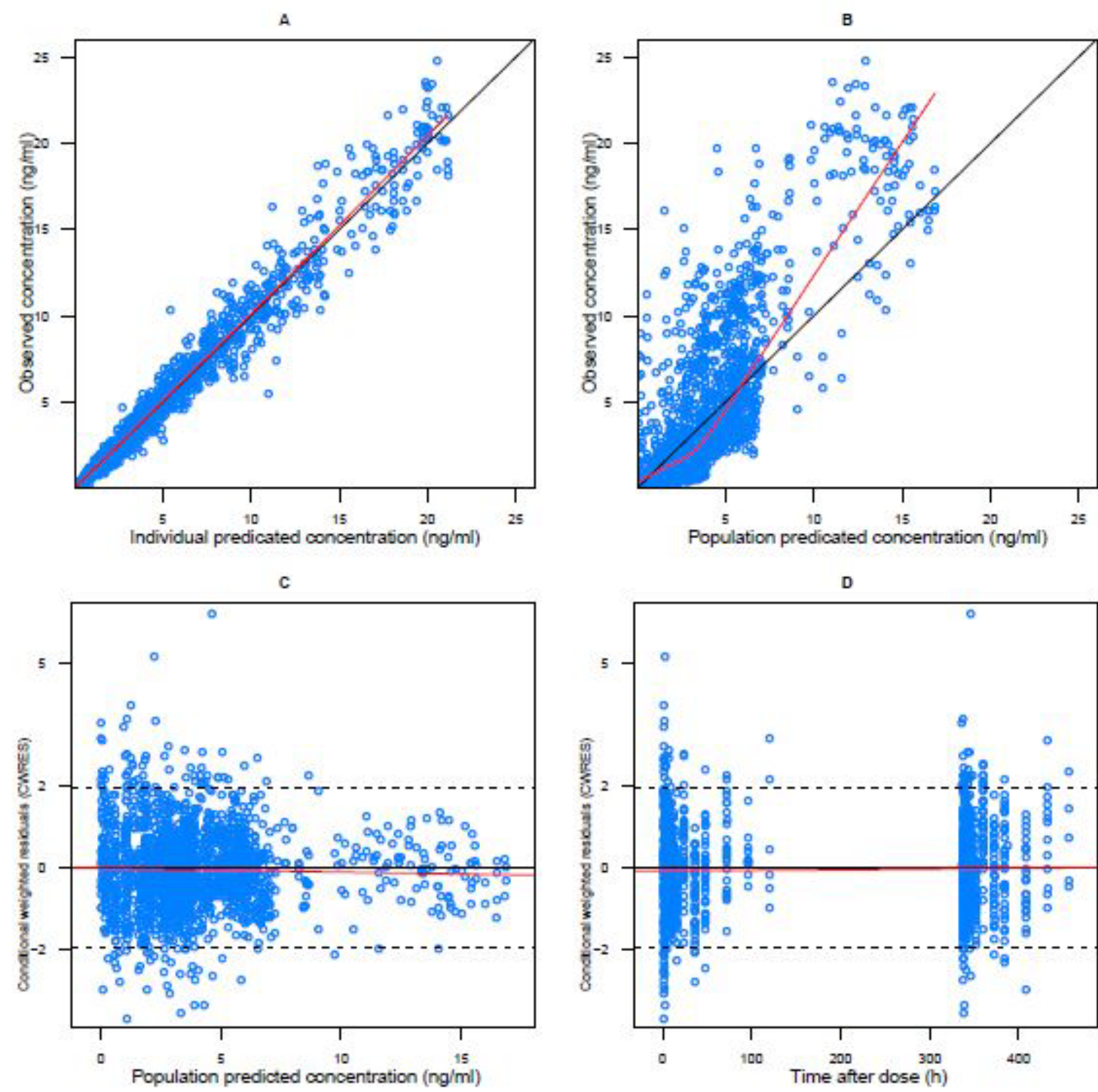


Fig. 2. Goodness of fit plots. A. observed concentrations versus individual predictions (IPRED); B. observed concentrations conditional versus population predictions (PRED); C. weighted residuals (CWRES) versus population predictions; D. conditional weighted residuals (CWRES) versus time after paroxetine dose

Discussion

- The main reason of selecting this model is because paroxetine is not only a substrate of CYP2D6, but also a strong inhibitor/inactivator of CYP2D6. A change in the amount of active enzyme by the inhibitor can result in a change in the intrinsic clearance and determines the nonlinear kinetic character of paroxetine itself.
- However, it also showed some underprediction for high concentrations (**Figure 2**).
- Simulations done with regard to enzyme parameters as well as clearance according to respective alleles were unsuccessful. Further refinements of the model will be considered.

Conclusion

The current model describes paroxetine nonlinear kinetics process to a certain extent.

¹ Sindrup SH, et al. Clin Pharmacol Ther. 1992; 51(3): 278-87.

² Zhang X, et al. Drug metabolism and disposition. 2009; 37, 1587-1597.

³ Sara K, et al. Drug metabolism and disposition. 2010; 38, 241-248.

⁴ Gaedigk et al. Clinical pharmacology and therapeutics. 2008;83(2):234-42.