

Autoinduction of phenytoin hepatobiliary secretion as a mechanism for its nonlinear pharmacokinetics

Alvariza S., Ibarra M., Vázquez M., Fagiolino P.
Department of Pharmaceutical Sciences, Faculty of Chemistry
Universidad de la República, Uruguay
salvariza@fq.edu.uy mibarra@fq.edu.uy

BACKGROUND

Phenytoin (PHT) is a first-line anticonvulsant widely used in the treatment and prophylaxis of seizures and different types of epilepsy. PHT pharmacokinetic response has been deeply studied due to its non-linear disposition produced by a concentration-dependent clearance, traditionally associated to a limited enzymatic capacity at drug therapeutic levels. This theory, however, has shown some inconsistencies with experimental observations. In this work, an alternative model including drug enterohepatic cycling was implemented in order to understand the nonlinear pharmacokinetic behavior of PHT. PHT and its main metabolite, p-hydroxyphenytoin (HPPH), observations were described and compared with the classic saturable elimination model.

METHODS

Eight healthy volunteers (6 men and 2 women) received orally 600 mg of PHT every 72 hours during a 10-day period (four dosing events at day 1, 4, 7 and 10). An immediate release tablet containing 100 mg of PHT was used (Comitoina, Roemmers Laboratories). In order to prevent loss of bioavailability due to PHT limited solubility in gastrointestinal fluids, each dose of 600 mg was divided in three administrations of 200 mg every 2 hours. Plasma levels of PHT and HPPH were measured at day 1 (12 and 24 hours post-dose) and at day 10 (20 samples obtained between 0 and 96 hours post-administration). Pharmacokinetic analysis was performed using NONMEM® 7.3 [1]. Structural and statistical models were evaluated with goodness of fit plots and Akaike information criterion.

RESULTS

Figure 1. Structural model considering PHT enterohepatic circulation

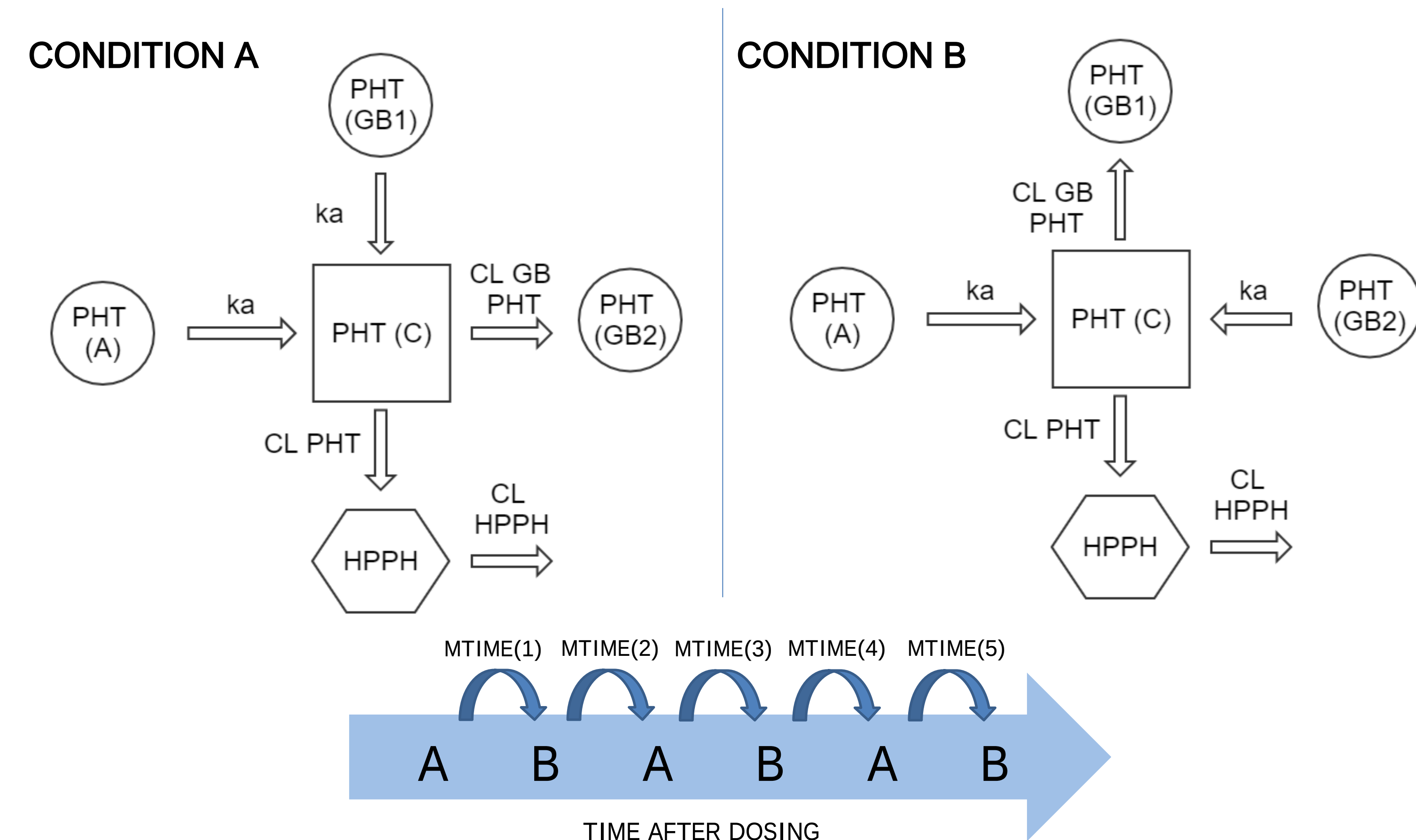


Table 1. Parameter estimates from bootstrap (n=200).

Parameter	Units	Estimate (%RSD)	IIV (%RSD)	Shrinkage	Comments
CL _{PHT} max*	L/h	2.28 (19.1)	53.7% (84.7)	0%	Final PHT elimination oral CL
CL _{PHT} base*	L/h	1.73 (23.1)	60.6% (108)	16 %	Initial PHT elimination oral CL
V _{PHT} *	L	54.1 (12.1)	28.7% (60.8)	0%	Apparent PHT volume of distribution
ka	h ⁻¹	0.299 (32.6)	81.5% (91.8)	0.7%	PHT absorption/reabsorption constant rate
CL _{PHT} GB max*	L/h	1.05 (36.0)	69.5% (82.0)	8.9%	Final PHT secretion CL into GB
CL _{HPPH} max*	L/h	98.1 (21.2)	44.7% (139)	0%	Final HPPH elimination oral CL
V _{HPPH} *	L	2450 (60.6)	174% (78.8)	0%	Apparent HPPH volume of distribution
Res _{PHT}	mg/L	0.325 (42.1)	---	7.2%	Additive PHT residual error
Res _{PHT}	mg/L	1.07 (18.6)	---	4.1%	Additive PHT residual error for absorption phase (until 16 h post-dose)
Res _{HPPH}	%	44.4 (15.8)	---	3.6%	Proportional HPPH residual error

*Median population estimates reported for 70 kg of body weight.

- Fraction of HPPH produced by PHT elimination was fixed to 1.
- PHT enterohepatic cycling was included in order to account for observed multiple-peaks in plasma using a previously published model [2]. Recirculation events were included for each administration every 12 hours starting from 20 h post-dose.
- Increase in CL_{PHT}, CL_{PHT} GB and CL_{HPPH} from day 1 to day 10 was included in accordance to observations and reported PHT inductive properties [3]. Model for CL_{PHT} induction: $CL_{PHT} = CL_{PHTmax} - (CL_{PHTmax} - CL_{PHTbase}) * \exp(-k_i * t)$. Induction constant rate (k_i) was fixed to 0.02 h⁻¹.

CONCLUSION

A model including PHT recirculation best-described observed PHT and HPPH data. In other dosage regimens, autoinduction of PHT recirculation could explain the decrease in systemic elimination and therefore its nonlinear accumulation.

Table 2. Parameter estimates from bootstrap for Michaelis-Menten model (n=200)

Parameter	Units	Estimate (%RSD)	IIV (%RSD)	Shrinkage	Comments
V _{MAX} PHT*	mg/h	21.6 (57.5)	32.3% (74.1)	0%	Maximum rate for PHT elimination
k _M PHT	mg/L	5.22 (86.2)	---	---	PHT concentration at which elimination rate is V _{max} /2
V _{PHT} *	L	73.4 (9.67)	18.7% (56.7)	3.6%	Apparent PHT volume of distribution
ka	h ⁻¹	0.500 (25.4)	91.4% (61.2)	7.3%	PHT absorption/reabsorption constant rate
CL _{HPPH} max*	L/h	110 (31.7)	43.9% (127)	0%	Final HPPH elimination oral CL
V _{HPPH} *	L	997 (62.5)	54.7% (291)	30%	Apparent HPPH volume of distribution
Res _{PHT}	mg/L	0.510 (72.6)	---	5.6%	Additive PHT residual error
Res _{PHT}	mg/L	1.10 (33.0)	---	4.4%	Additive PHT residual error for absorption phase (until 16 h post-dose)
Res _{HPPH}	%	46.5 (18.5)	---	3.4%	Proportional HPPH residual error

Figure 2 Goodness of fit plots for enterohepatic cycling model. **AIC = -500**

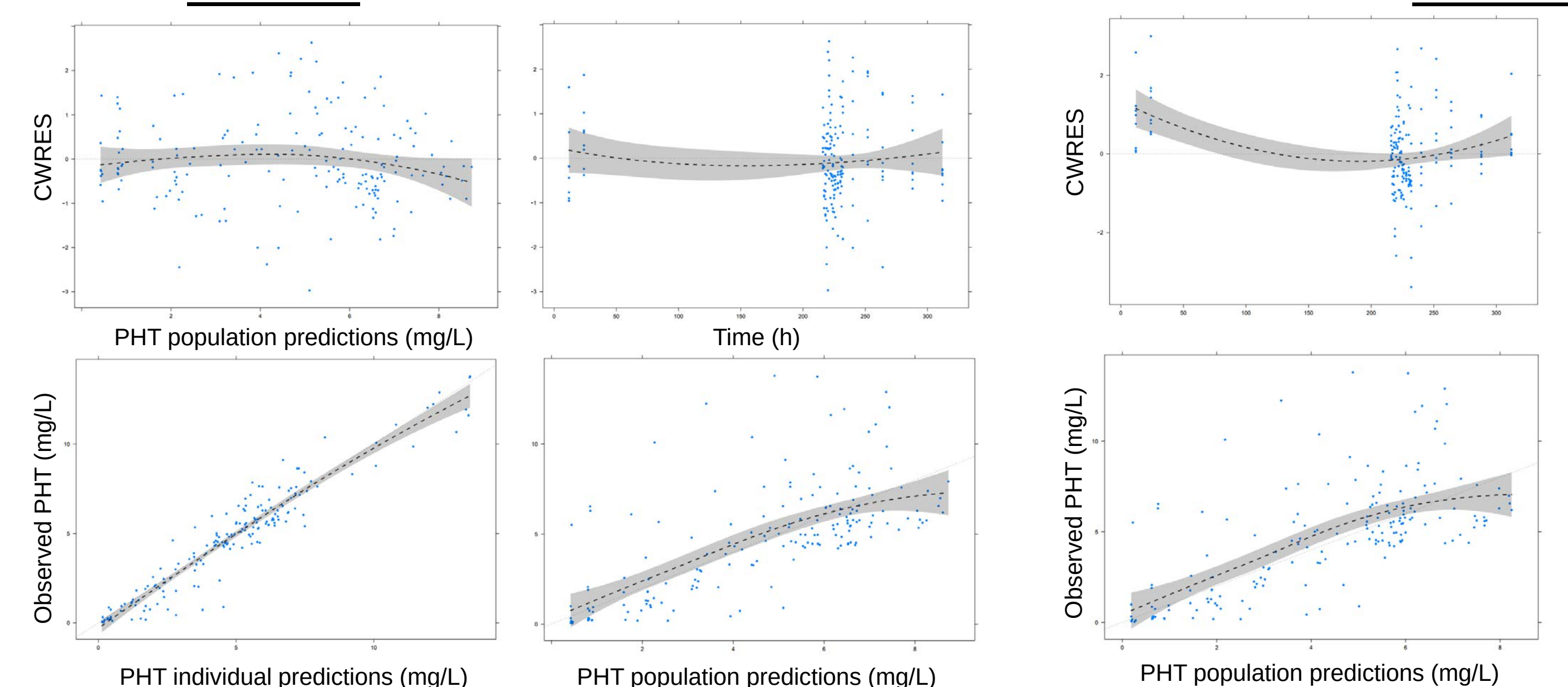
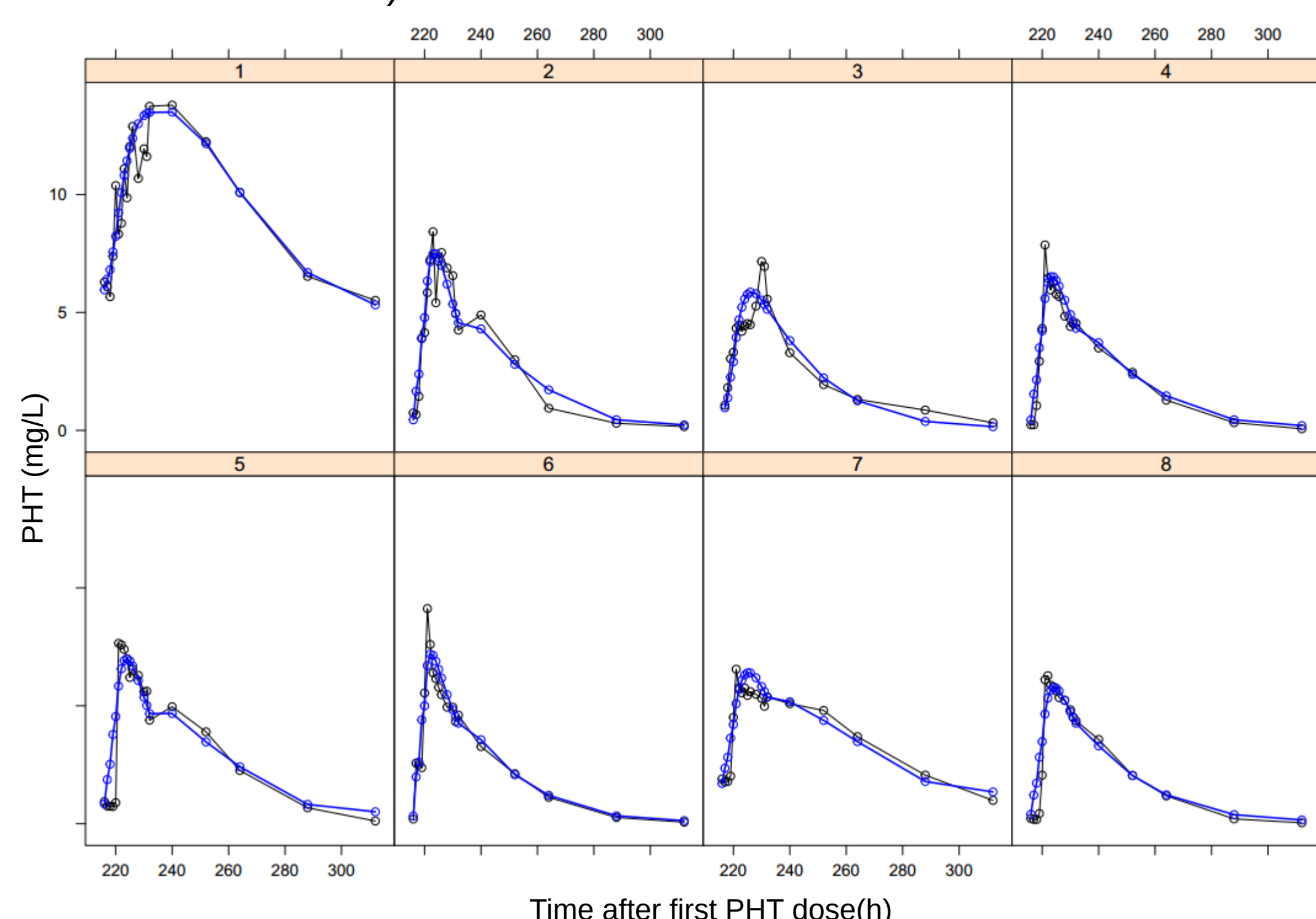


Figure 3 Goodness of fit plots for Michaelis-Menten model. **AIC = -467**

Figure 4 Individual fits for PHT recirculation model. Observed (black) and predicted (blue) PHT plasma concentrations versus time from day 10th (4th PHT administration).



- Mean estimated fraction of PHT submitted to enterohepatic cycling at steady state: 32%.
- HPPH disposition rate-limited by PHT metabolism.

REFERENCES

- Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J. NONMEM User's Guides 1989-2009; Icon Development Solutions, Ellicott City, MD, USA, 2009
- Ibarra, M., Vazquez, M., Fagiolino, P. Population pharmacokinetic model to analyze nevirapine multiple peaks profile after a single oral dose. JPKPD 2014; 41(4).
- Alvariza, S., Fagiolino, P., Vazquez, M., Feria-Romero, I., Orozco-Suarez, S. Chronic administration of phenytoin induces efflux transporters overexpression in rats. Pharmacological Reports 2014; 66.