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AGE INFLUENCE ON CLEARANCE OF PHENOBARBITAL IN PAEDIATRIC PATIENTS

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OBJECTIVE

To describe the influence of AGE on phenobarbital (PBT) clearance (CL/F_{PBT}) developing a pharmacokinetic (PK) model in a paediatric population.

METHODS

MODEL DEVELOPMENT

NONMEM V7.2 (FOCEI, ADVAN2 TRANS2)
COV analysed:
AGE, WGT, HGT, BSA, BMI, LBM, SEX, diagnostic of epilepsy, concomitant treatment.
Covariate Model Building:
Stepwise forward inclusion (p = 0.05)
Backward exclusion (p = 0.001)
Missing data = missing completely at random (MCAR)

MODEL EVALUATION:

Bootstrap
Visual Predictive Check (VPC)
Numerical Predictive Check (NPC)

POPULATION & TREATMENT

PBT: oral administration
Concomitant treatments: phenytoin, lamotrigine, valproic acid, others
39 patients; **71 PBT serum concentrations** (at steady-state)

Table 1. Baseline patient characteristics

	Unit	N	Mean	SD	Percentile 25-75	Range
Male		21				
Female		18				
AGE	year	39	3.89	3.92	0.84 – 5.25	0.08 - 14
WGT	kg	39	17.41	13.65	7.70 – 20.00	3.9 - 65
HGT	cm	25	97.79	32.11	73.25 – 117.80	51 - 157
BMI	mg/m^2	25	17.99	7.71	14.56 – 20.17	7.81 – 49.93
BSA	m^2	25	0.68	0.37	0.37 – 0.83	0.22 – 1.65
LBM	kg	25	15.03	10.54	5.44 – 13.16	3.31 – 44.18

N, number of patients; SD, standard deviation; WGT, weight; HGT, height; BMI, body mass index; BSA, body surface area; LBM, lean body mass

RESULTS

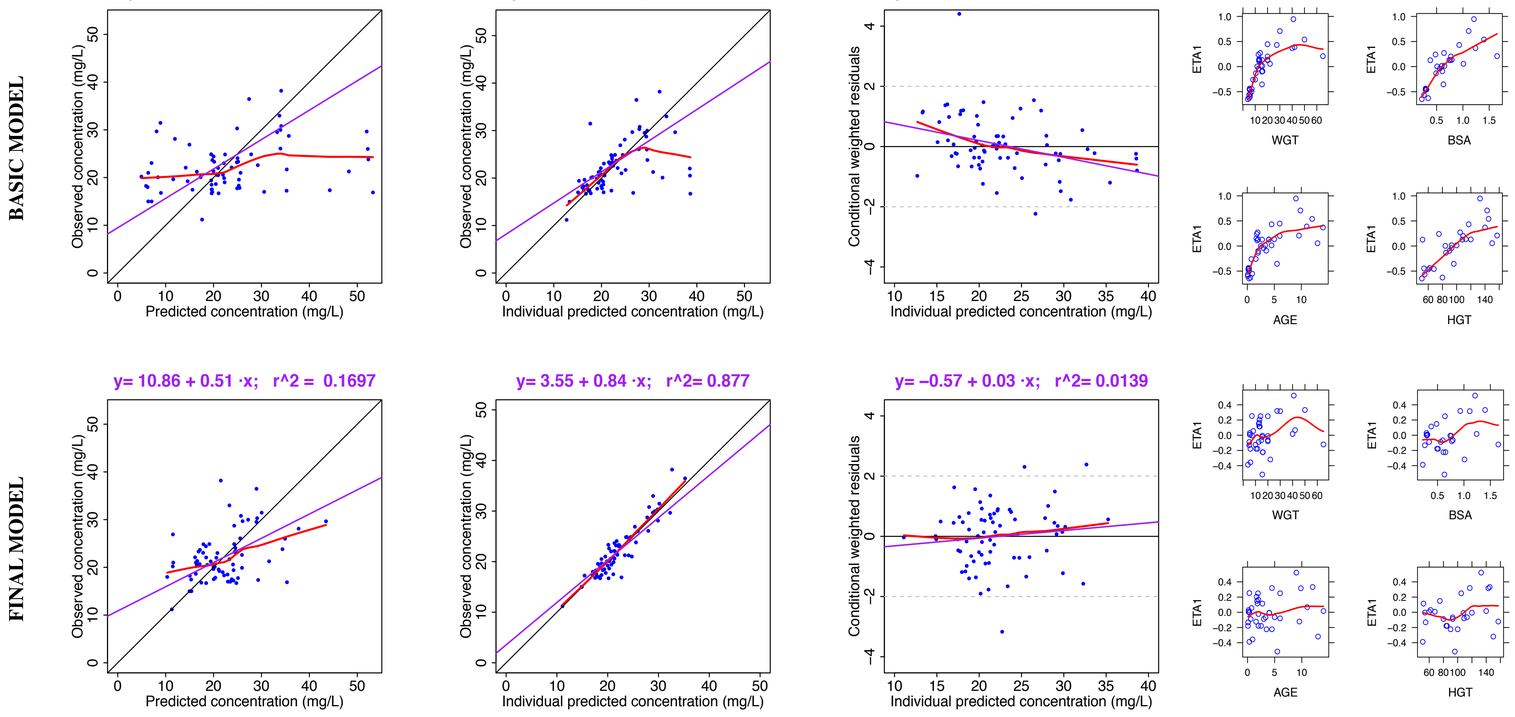

Figure 1. Basic of goodness of fit plots for the basic and final model of phenobarbital in paediatric population; Covariates vs interindividual variability of CL/F_{PBT} (ETA1); purple lines and text, regression lines by using ordinary least square method; red lines, regression lines by using locally-weighted polynomial regression.

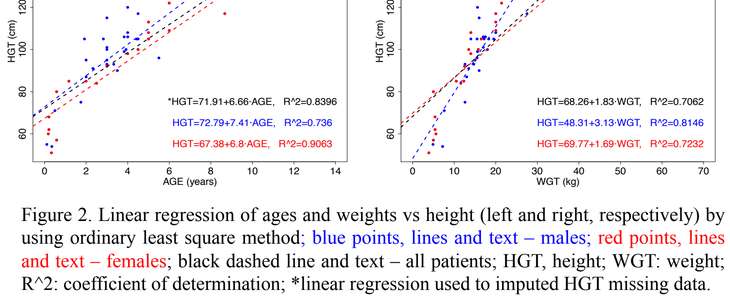

Figure 2. Linear regression of ages and weights vs height (left and right, respectively) by using ordinary least square method; blue points, lines and text – males; red points, lines and text – females; black dashed line and text – all patients; HGT, height; WGT: weight; R^2: coefficient of determination; *linear regression used to imputed HGT missing data.

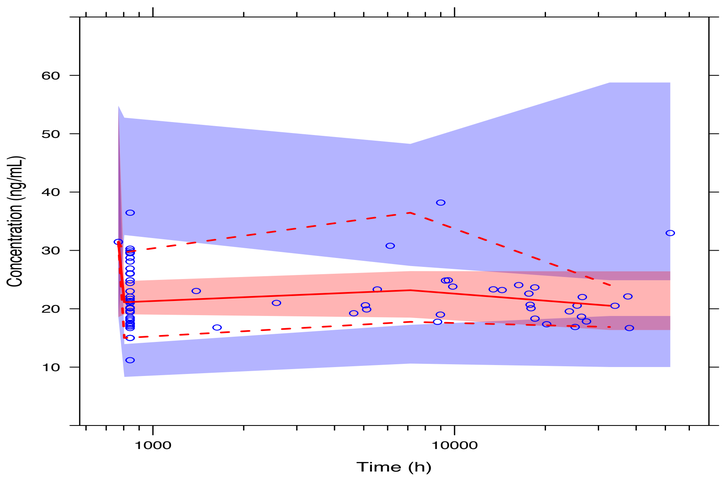

Figure 3. VPC (n=200) of the popPK final model. Blue circles, observed concentrations; red solid line – median of the observed concentrations; red dashed line - 5th and 95th percentile of observed concentrations; red shaded area – 95% confidence interval for the 50th percentile of the simulated data; blue shaded areas – 95% confidence intervals for the 10th and 90th percentiles of simulated data.

Table 2. Pharmacokinetic parameters of the final model

Parameter	Estimated value	RSE (%)	Shrinkage (%)	Bootstrap (n=500)	
				Median	95% CI
Θ_1	0.179	17	.	0.209	0.137-0.382
Θ_2	0.900	.	.	0.900	0.900-0.900
Θ_3	-0.129	23	.	-0.160	(-0.312)-(-0.093)
Θ_4	-0.240	43	.	-0.254	(-0.572)-(-0.053)
Θ_5	0.647	9	.	0.656	0.523-0.897
$\eta_{CL/F}$*	0.053	25	5	0.049	0.024-0.079
ε*	0.012	30	28	0.012	0.007-0.018

Θ_n, fixed effect parameters; RSE, relative standard error; CI, confidence interval; *Proportional error model; $\eta_{CL/F}$, random effect parameter; ε, residual variability.

$A=\Theta_1$
$B=\Theta_3 \cdot e^{(AGE \cdot \Theta 4)}$
$C=\Theta_5^{VLP}$
$TVCL=(A+B) \cdot C$
$CL=TVCL \cdot (1+(\eta_1))$
$V=\Theta_2 \cdot (WGT)$
$Ka=1.33$
$K=CL/V$

FINAL MODEL

$CL/F= (0.179\text{-}0.129 \cdot e^{-AGE \cdot 0.24}) \cdot 0.647^{VLP}$
$V= 0.9$ L/kg; $Ka=1.33$ h^{-1}

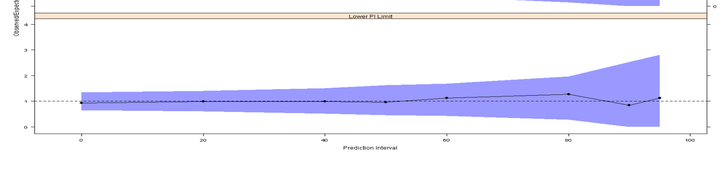

Figure 4. NPC (n=200) of the popPK final model. PI, prediction interval; Black solid line, median of the ratio observed/expected data at the PI 5, 20, 40, 60, 80, 90 and 95%; Blue shaded area – 90% prediction interval of the observed/expected data calculated from simulations.

CONCLUSIONS

A suitable population PK model of PBT in paediatric patients has successfully been developed. The final model showed an important influence of AGE on the CL/F_{PBT}. Concomitant valproic acid treatment was included following statistics criteria (ΔOFV=-13.5) despite the fact that there were only 10% of the population. The inclusion of AGE and valproic acid treatment have reduced the clearance interindividual variability and residual variability in a 48% and 57%, respectively. Consequently, its real influence should be evaluated again with a more representative set of data of this covariate. The model proposed is useful for raising awareness of the PK of this drug in childhood and could be helpful for TDM using a Bayesian approach.

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