

A population pharmacokinetic model for propofol in (pre)term neonates and infants independently accounting for size, gestational age and postnatal age.

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BACKGROUND

- Propofol (Diprivan®) is frequently used for induction and maintenance of anesthesia and procedural sedation in (pre)term neonates and infants.
- Being a UGT1A9 and CYP2B6 substrate, maturational on top of scale effects have to be accounted for to describe the pharmacokinetics in this population.
- The current population PK models fall short in terms of suitability for extrapolation, plausibility and/or predictive capacity in the target population [1-3].

OBJECTIVES

- Demonstrate that independently accounting for intrauterine age (GA) and postnatal age (PNA) instead of aggregation of these metrics into postmenstrual age (PMA) improves the description of the pharmacokinetics of propofol in (pre)term neonates and infants.

METHODS

- Pooled analysis data from 3 previously published studies (Allegaert 2007 [1], Smits 2016 [4] (PK unpublished) and Sepulveda 2011 [5]).
- The final dataset included 107 individual PK profiles (837 arterial samples).
- Relevant patient demographic/anthropometric and clinical data were collected prospectively (Table 1).
- Data were analyzed with nonlinear mixed effects modeling (Monolix 2018R2).

Table 1. Clinical demographics of the final analysis data

Covariate (unit)	Value (range)
TBW (kg)	3.050 [0.580 – 11.440]
PMA (weeks)	38.00 [25.00 – 142.00]
GA (weeks)	37.14 [24.57 – 40.14]
PNA (weeks)	1.14 [0 – 104.00]
GENDER (0 = female, 1 = male)	0 = 37, 1 = 70
NEO (0 = infant, 1 = neonate)	0 = 41, 1 = 66
PRE (0 = term, 1 = preterm)	0 = 54, 1 = 53

- Several models with ascending complexity were tested, model evaluation was performed based on objective function values (OFVs) (-2.log likelihood (-2LL) and Akaike information criterion (AIC)), standard errors of the population parameter estimates and diagnostic plots (prediction corrected visual predictive checks (pcVPC) (Figure 1), population goodness of fit (pGoF) (Figure 2), population weighted residuals in function of time (PWRES) (Figure 2) and distributions of the random effects).
- Propofol clearance maturation (Figure 3) was accounted for via different maturation terms (MAT) on top of the fixed allometric scaling factor:

$$\theta_{CL,i} = \theta_{CL,pop} \cdot \left(\frac{TBW}{70}\right)^{0.75} \cdot MAT \cdot e^{\eta_{\theta,i}}$$

RESULTS

- A three compartment structural model adequately described the data.
- Allometric scaling with fixed exponents was applied to all parameters [6]:

$$\theta_i = \theta_{pop} \cdot \left(\frac{TBW}{70}\right)^a \cdot e^{\eta_{\theta,i}}$$

(a fixed to 0.75 for clearances and 1 for volumes)

- The final maturation term selected accounted independently for GA and PNA:

$$MAT_{GA,PNA} = GMAX \cdot \left(\frac{GA}{38}\right)^b + (1 - GMAX) \cdot \left(1 - e^{-\frac{\ln(2) \cdot PNA}{T_{1/2}^a}}\right)$$

- V₁ negatively correlated with age (Figure 3). A covariate effect of PNA on V₁ was added to the model, which further improved the fit:

$$V_{1,i} = V_{1,70,pop} \cdot \left(\frac{WT \cdot e^{\left(\frac{PNA}{52 \cdot \beta_{V_1}}\right)}}{70}\right) \cdot e^{\eta_{V_1,i}}$$

- Parameter estimates, estimate precision and inter-individual variability (IIV) are reported in Table 2. Extrapolation to 70kg yields plausible parameter values.
- The final maturation term reduced the unexplained inter-individual variability in this population for clearance from 227.8 % for the allometrically scaled weight-proportional model to 39.4% for the final maturation model.

CONCLUSIONS

- Independently accounting for intrauterine (GA) and postnatal (PNA) maturation improves the description of propofol pharmacokinetics in a mixed (pre)term neonatal population.
- The final model allows for extrapolation to adult parameter (especially clearance) values, which are in line with results from adult popPK studies.
- The age-effect on V1 is most likely caused by changes in body composition with age in this population (e.g. changes in total body water and proportion of fat free mass).
- Development of algorithms to formalize the estimation of body composition predictors down to neonatal age range similar to those available in older children (e.g. Al-Sallami *et al.*: FFM in children 3 to 29 years [7]) are crucial to improve the predictive properties of (population) pharmacokinetic models across the pediatric population.

Table 2. Pharmacokinetic parameter estimates of the final population pharmacokinetic model.

Parameter	Estimate (unit)	RSE (%)	IIV (CV%)	RSE (%)
CL	1.56 (L min ⁻¹ 70 kg ⁻¹)	5.97	39.4	8.6
V ₁	19.8 (L 70 kg ⁻¹)	8.18	29.8	34.1
Q ₂	4.16 (L min ⁻¹ 70 kg ⁻¹)	6.19	38.0	13.1
V ₂	41.9 (L 70 kg ⁻¹)	3.94	22.3	15.8
Q ₃	0.511 (L min ⁻¹ 70 kg ⁻¹)	6.26	45.8	10.9
V ₃	246 (L 70 kg ⁻¹)	8.14	54.9	11.6
GMAX	0.334	14.5		
b	7.98	8.28		
T _{1/2} ^a	4.43	12.7		
β _{V₁}	0.718	12.5		
Residual error	0.142	3.65		

RSE: residual standard error; IIV: interindividual variability; CV%: percentual coefficient of variation, calculated as the square root of the exponential variance of η minus 1; GMAX: partition coefficient; b:exponential scaling factor on GA; T_{1/2}^a: PNA half-life; β_{V₁}: scaling coefficient of PNA on V1 covariate effect. Combined residual error model: estimated proportional term, fixed additive term (to 0.004).

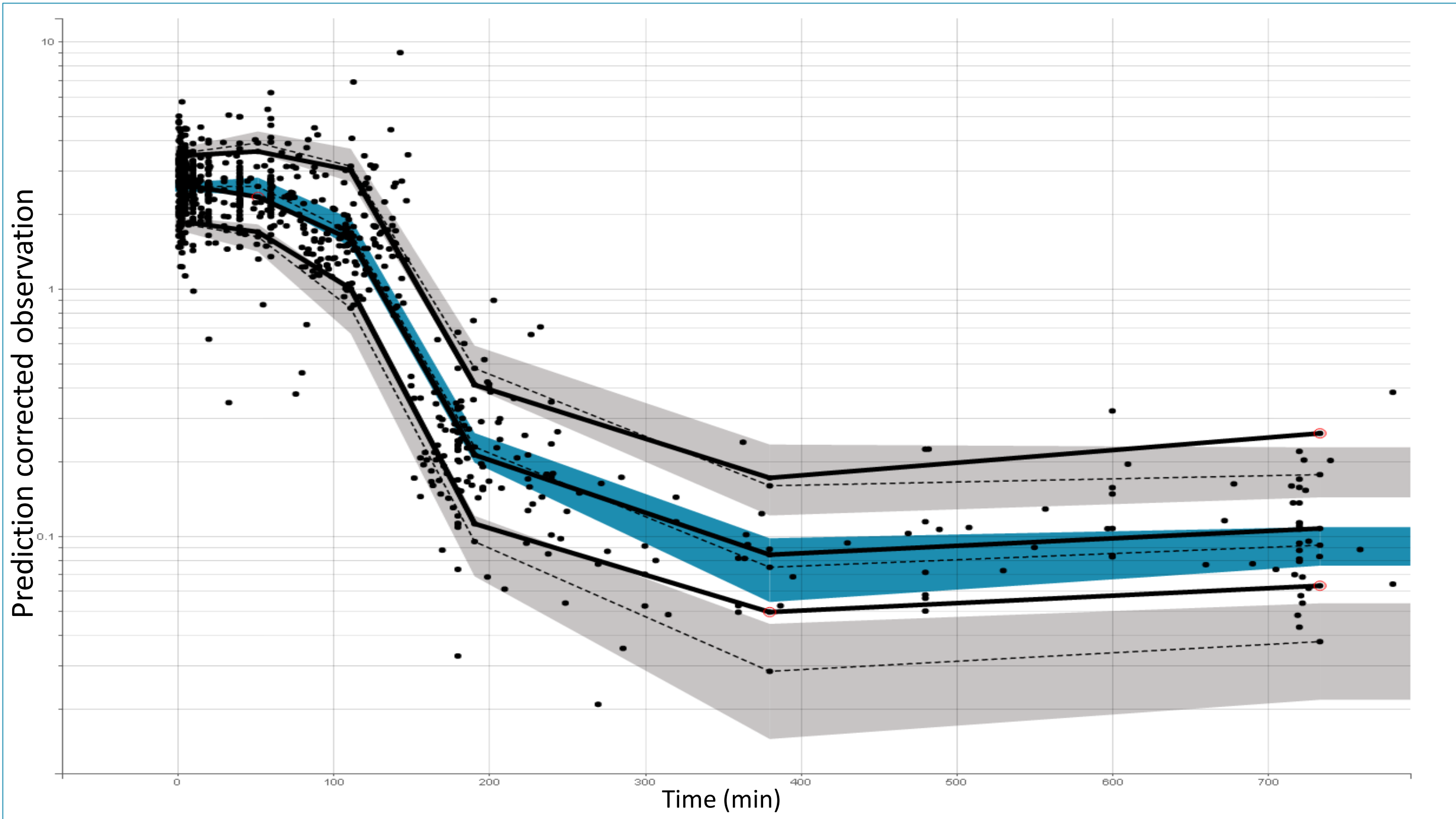


Figure 1. Prediction corrected VPC (pcVPC) plot. Lower grey area: 90% prediction interval of the 10th percentile. Middle blue area: 90% prediction interval of the 50th percentile. Upper grey area: 90% confidence interval of the 90th percentile. Dotted black lines are the predicted percentiles. Full black lines are the empirical percentiles.

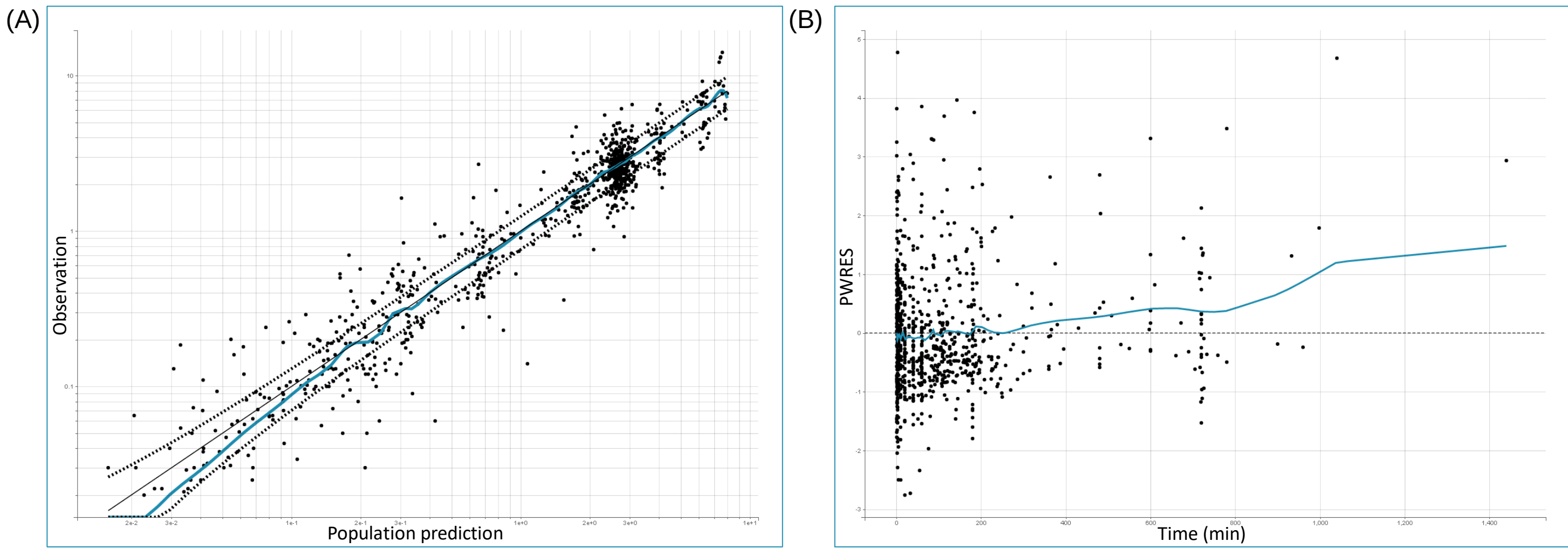


Figure 2. (A) Goodness of Fit (GoF) plot: observation in function of population prediction. Black dotted line: 90% prediction interval. Blue line: spline. (B) Population weighted residuals in function of time. Blue line: spline.

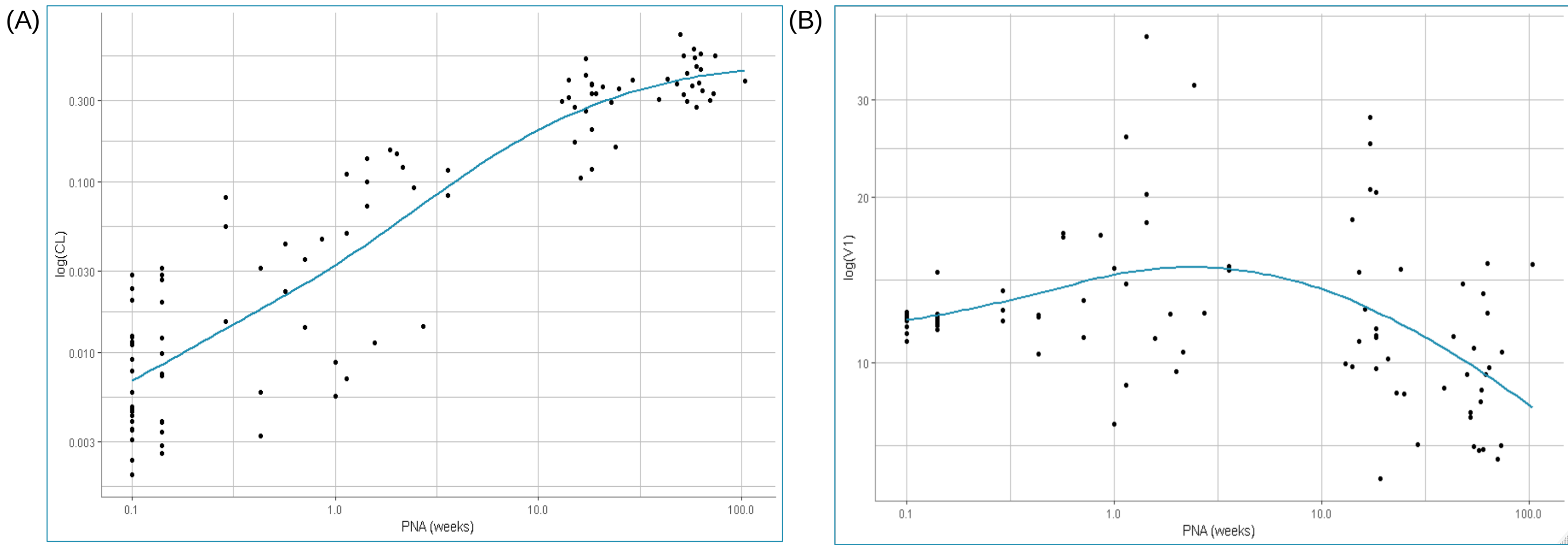


Figure 3. (A) log(CL) in function of (log)PNA, clearance maturation is observed. (B) log(V₁) in function of (log)PNA. Blue line: spline.