Population Pharmacokinetic Modeling of Free Phenytoin in Adult Patients: Clinical Factors Affecting Protein Binding

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Background

- Phenytoin (PHT) is a widely used anticonvulsant with a narrow therapeutic window (10-20 μg/mL for total, 1-2 μg/mL for free PHT concentrations)[1].
- Routine therapeutic drug monitoring (TDM) is recommended to ensure efficacy and reduce toxicity.
- Free PHT concentrations are not always measured due to cost or lack of available assay.
- TDM of PHT is commonly conducted by measuring total concentrations. Free concentrations are often estimated with regression equations such as the Winter-Tozer equation[1].
- PHT is extensively bound to albumin (~90%)[2] and exhibits high inter-individual variabilities in free fraction[3].
- A full population pharmacokinetic model describing the protein binding properties of free PHT in adults is still lacking.

Objective

- To develop and validate a comprehensive population pharmacokinetic model describing the pharmacokinetic characteristics and protein binding properties of free PHT in adult patients.

Study Design and Methods

- The study was approved by the University of British Columbia (H18-02215) and the University of Alberta Research Ethics Boards (Pro00100357).
- Retrospective study enrolling subjects from year 2014 to 2018 in a tertiary hospital in Vancouver, Canada.
- Paired total and free steady-state PHT concentrations from 37 adult patients receiving oral (n=21) or intravenous (n=16) PHT therapy.
- Non-linear mixed-effects modeling was conducted using stochastic approximation expectation-maximization algorithm in MonolixSuite-2019R2.
- **Population-pharmacokinetic base model selection:** The best structural, error, and co-variate models were selected based on objective function values, relative standard errors (RSEs), and biological plausibility.
- **Population-pharmacokinetic model evaluation:** Established model was internally evaluated using goodness-of-fit plots, visual predictive checks, and bootstrapping analysis.

Table 1. Patient demographics (n=37).

Parameter	Median	Mean ± SD
Age (years)	62	61.1 ± 17.9
Critical care (Y/N)[a,b]		16/21
Sex (female/male)[a]		10/27
Weight (kg)	70	68.5 ± 15.6
Albumin (g/dL)	2.7	2.6 ± 0.5
Serum creatinine (mg/dL)	0.9	1.1 ± 1.0
Alanine aminotransferase (U/L)	36	71.6 ± 116.2
Aspartate aminotransferase (U/L)	28	42.8 ± 37.1
Bilirubin (mg/dL)	0.4	0.9 ± 2.3
International normalized ratio (INR)	1.0	1.1 ± 0.1
Hemodialysis (Y/N)[a,c]		1/34
Current medications[a,c]		
Aspirin (Y/N)		10/26
Carbamazepine (Y/N)		1/23
Heparin (Y/N)		1/34
Phenobarbital (Y/N)		1/34
Sulfonamides (Y/N)		1/34
Valproic acid (Y/N)		2/33
Warfarin (Y/N)		1/34
PHT dosage and measurements		
PHT dose (mg/day)	300	378.5 ± 148.3
Administration route (IV/PO)[a]		16/21
Total PHT concentration (μg/mL)	9.8	11.4 ± 5.3
Free PHT concentration (μg/mL)	1.1	1.4 ± 0.7
Free fraction (%)	11.8	12.4 ± 3.1

IV, intravenous; PO, oral; SD, standard deviation.
[a]Categorical data are expressed as counts.
[b]Patients are considered under "critical care" when admitted to either the general or neurosurgical intensive-care unit.
[c]Records were missing in some patients.

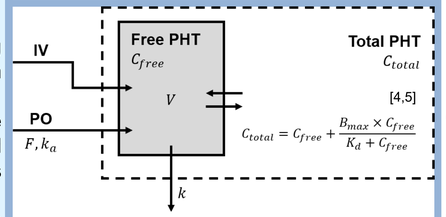

Figure 1. Structural model of phenytoin.
Bmax, binding constant; Cfree, free PHT concentration; Ctotal, total PHT concentration; F, bioavailability; k, elimination rate constant; ka, absorption rate constant; Kd, dissociation constant; V, volume of distribution.

Table 2. Population parameter estimates.

Parameters	Estimated mean value (RSE%)	η-shrinkage (%)	Bootstrap mean (95% CI)
Fixed effects			
F	0.859 fixed		
ka (hr^{-1})	0.225 fixed		
V (L)	102 (11.5)		102 (60.9-200)
k (hr^{-1})	0.0267 (9.03)		0.0267 (0.0127-0.0428)
Bmax (μg/mL)	154 (26.7)		154 (86.8-381)
$\beta^{albumin}$_Bmax	0.679 (23.6)		0.679 (0.417-1.08)
β^{INR}_Bmax	-0.626 (40.5)		-0.626 (-1.03 to 0.170)
Kd (μg/mL)	9.16 (5.28)		9.16 (6.74-21.5)
Inter-individual variability			
ω_V	0.460 (13.0)	0.847	0.460 (0.127-0.512)
ω_k	0.164 (54.9)	-4.92	0.164 (0.100-0.574)
ω_Bmax	0.0725 (49.8)	12.8	0.0725 (0.0233-0.151)
ω_Kd	0.130 (43.2)	-9.23	0.130 (0.0433-0.193)
Residual variability			
b1	0.0227 (67.1)		0.0227 (0.00720-0.0311)
b2	0.0627 (77.2)		0.0627 (0.0235-0.114)

b1, proportional error for total PHT concentrations; b2, proportional error for free PHT concentrations; β, co-variate parameter estimate; CI, confidence interval; ω, inter-individual variability.

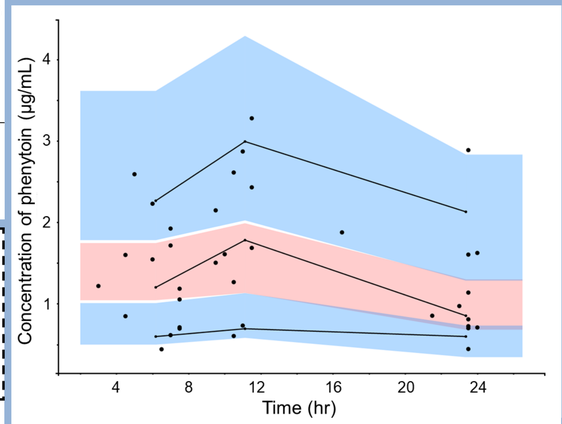

Figure 2. Prediction-corrected visual predictive check of free PHT concentrations.
Individual plasma concentrations of free PHT (·); 5th, median, and 95th empirical percentiles (—); 5th and 95th percentiles (blue) or median (pink) prediction interval areas based on 1000 simulations.

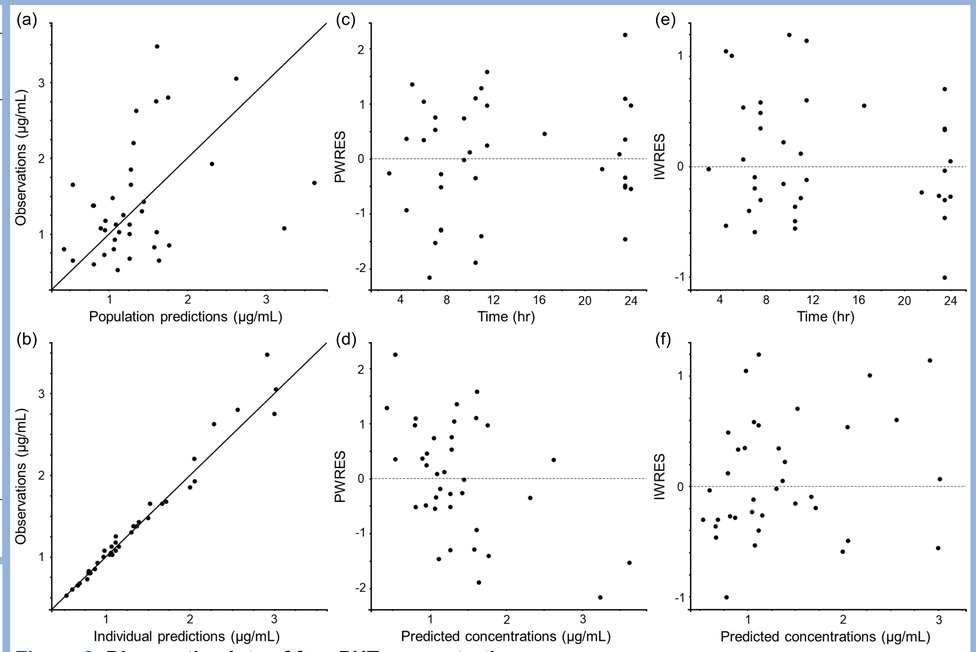

Figure 3. Diagnostic plots of free PHT concentrations.
(a) Observed plasma concentration of free PHT (OD) vs. population predicted concentration (PRED); (b) OD vs. individual predicted concentration (IPRED); (c) population-weighted residuals (PWRES) vs. time; (d) PWRES vs. PRED; (e) individual-weighted residuals (IWRES) vs. time; (f) IWRES vs. IPRED

Results & Conclusions

- A one-compartment, intravenous injection/first-order absorption, and first-order elimination model with proportional errors best described the population kinetics of PHT (Figure 1).
- The protein binding characteristics of PHT was optimally modelled by a single site, non-linear binding equation characterized with a binding constant and a dissociation constant[4,5] (Figure 1).
- Further research on additional protein binding models with a variety of elimination processes is ongoing.
- Albumin (positive effect) and INR (negative effect) independently affected Bmax (Table 2).
- This model can be utilized to construct Bayesian forecasting engines for therapeutic drug monitoring of PHT in adult population.

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