Population Pharmacokinetics and Sources of Variability of Free Phenytoin Concentrations

Jordan Ho, B.Sc.(Pharm); Yan Rong, B.Sc.; Wendy Cheng, B.Sc.(Pharm), ACPR; Catharina Yih, B.Sc.(Pharm), ACPR; Tony Kiang, B.Sc.(Pharm), PhD, ACPR

Background

- Phenytoin (PHT) is a common medication for treatment and prevention of seizure, exerting its pharmacological effect through the free drug fraction in the blood.
- Several equations and models are available to predict free PHT concentration (e.g. Winter-Tozer equation)
- Studies have assessed this equation and reported inconsistent findings on bias (e.g. overprediction or underprediction) and precision with regards to the actual free PHT concentration.
- The best approach for determining free PHT concentration is to develop a population pharmacokinetic model (PPK), which allows for a more dynamic approach than the traditional, static, Winter-Tozer equation.
- Population modeling with the Bayesian feedback approach was used in populations in Africa, Saudi Arabia and Japan, to guide clinical decision making for phenytoin dosing.

Objectives

- To develop and validate a non-linear mixed-effects model to predict the PPK of PHT, and the effects of co-variates in adult patients receiving PHT.

Methods

- A retrospective chart review was conducted via a convenience sample of adult patients with at least two measurements of free and total phenytoin concentrations. Patients were excluded if concentrations were below measurable limits or drawn in the emergency department.
- Demographics including weight, age and gender, lab values including SrCr and albumin, and interacting medications including valproic acid, aspirin, warfarin, sulfonamides, phenobarbital and carbamazepine were also collected.
- Non-linear mixed-effects modeling using stochastic approximation of the expectation maximization algorithm was conducted in Monolix (Lixoft, version 2018R2).
- Co-variates were selected based on Pearson's correlation test ($p<0.005$), coefficient of correlation ($R>0.5$), and overall objective function values.

Results

Table 1. Patient demographics (N = 39)

Parameters	Mean ± SD
Gender (Male/Female)	29/10
Age (years)	62 ± 18
Weight (kg)	69 ± 17
Albumin (g/L)	28 ± 6
SrCr (μmol/L)	74 ± 27

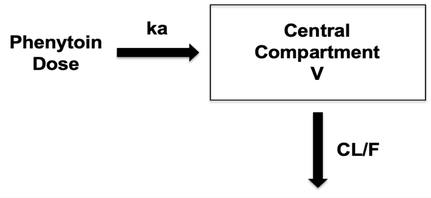
Data presented as mean ± SD. SrCr: serum creatinine

Table 2. Population pharmacokinetic parameter estimates for phenytoin

Parameters	Population Estimates (R.S.E (%))	Standard Deviation of the Random Effects (R.S.E (%))
ka (h^{-1})	0.807 (85.8)	1.42 (57.7)
CL/F (L/h)	6.45 (68)	0.431 (63.1)
V (L)	10.7 (19.7)	0.69 (37.2)

R.S.E.: relative standard error, ka: absorption rate constant, CL/F: apparent oral clearance, V: apparent central compartment volume of distribution.
Combined error model, error model parameter a = 2.47 (52.8), presented as population estimates (R.S.E(%)).

Figure 1. Free PHT PPK structural model

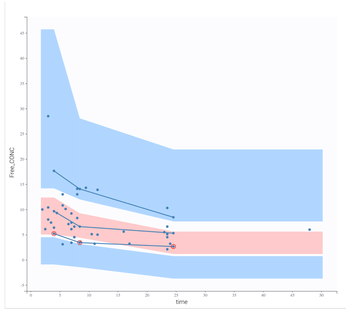


Equation 1. Covariates model of free concentrations of PHT

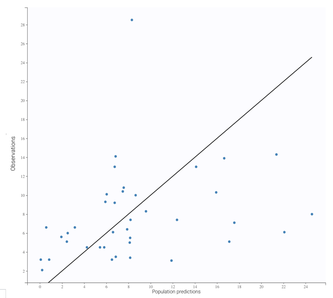
$$CL_{free}/F_i = 6.45 \times (\text{total concentration of phenytoin})_i^{-0.0384} \times e^{\eta_i}$$

Figure 2. Visual prediction check and goodness-of-fit plots

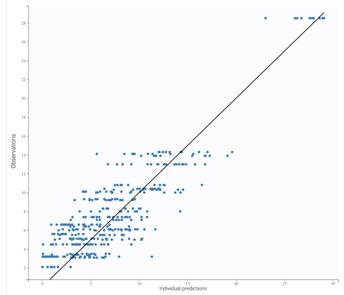
a. Visual prediction check



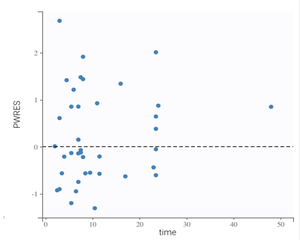
b. Observations vs predictions plot using population parameters



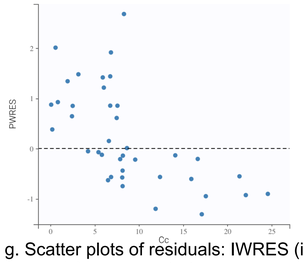
c. Observations vs predictions plot using individual parameters



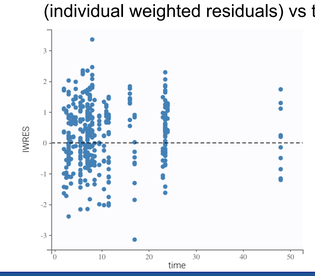
d. Scatter plots of residuals: PWRES (population weighted residuals) vs time



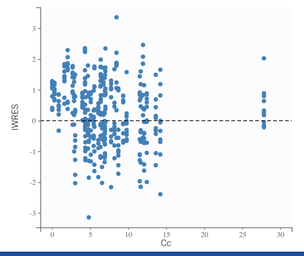
f. Scatter plots of residuals: PWRES (population weighted residuals) vs concentration



e. Scatter plots of residuals: IWRES (individual weighted residuals) vs time



g. Scatter plots of residuals: IWRES (individual weighted residuals) vs concentration



Conclusions

- The population pharmacokinetics of PHT is best illustrated by a **one-compartment, first-order absorption, and linear elimination** structural model of free PHT (with combined error model).
- The final population PK parameter values (mean estimate + standard error) were: ka (0.807±1.42 h^{-1}), CL/F (6.45±0.431 L/h), and V (10.7±0.69 L).
- We have developed/validated a novel population PK model for phenytoin in a population of adult patients at VGH. Further work is ongoing to establish a Bayesian forecasting model.
- Using the equation generated from our model, we are able to estimate free PHT clearance, and thus exposure to PHT, from total PHT concentration, regardless of albumin concentration.

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