

## ABSTRACT

### Objective:

This study aimed to assess the population pharmacokinetics of phenytoin in Saudi patients and identify factors affecting therapeutic parameters.

### Method:

A retrospective chart review was performed at King Saud University Medical City on patients treated with oral phenytoin. We used Monolix 4.4 for population pharmacokinetic modeling. A base model was developed to investigate several covariates, including age, gender, weight, total daily dose, and liver function test results.

### Results:

The analysis included a total of 81 phenytoin plasma concentrations from 43 patients (70% male). Patients' mean ( $\pm$ SD) age was 41 ( $\pm$ 18.7) years and body weight was 65.4 ( $\pm$ 17.7) kg. The patients received a phenytoin total daily dose (TDD) of 330.5 ( $\pm$ 104.5) mg/day, resulting in a trough concentration of 11.2 ( $\pm$ 10.3) mg/L. The data were sufficiently described by the one-compartment open model with linear absorption and non-linear elimination processes. Average parameter estimates for phenytoin  $V$ ,  $V_{max}$ , and  $K_m$  were 0.61 L/h/kg, 6.12 mg/kg/day, and 5.33 mg/L, respectively. The most significant covariates on phenytoin  $V_{max}$  and  $K_m$  were the age and body weight of the patients, along with valproic acid co-therapy.

### Conclusion:

The population pharmacokinetic model of phenytoin in Saudi patients found significant inter-individual variability between subjects, which was affected by the patients' age, body weight, and valproic acid co-therapy as the most significant covariates on phenytoin  $V_{max}$  and  $K_m$ . To provide guidance in drug dosage decisions, further studies are required to evaluate all factors that may potentially influence the pharmacokinetics of phenytoin.

## OBJECTIVES

The study objective was to estimate the pharmacokinetic parameters of phenytoin and identify the factors that are most closely associated with the therapeutic variability between individuals. This study aimed to provide guidance for optimizing phenytoin regimens in clinical practice.

## METHODS

### Patients and Data Collection

This was a retrospective study that used clinical data collected from stable patients with epilepsy who received phenytoin treatment. This study included all patients who were subjected to routine phenytoin therapeutic drug monitoring (TDM). The routine TDM samples were obtained from these patients during clinic visits for routine follow-up examinations. The characteristics collected for each patient were age, weight, gender, total daily dose (TDD), phenytoin trough concentration, serum creatinine concentration, total albumin concentration, total bilirubin concentration, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and concomitant antiepileptic agents. This study was approved by the IRB committee at King Saud Medical City.

## METHODS

### Sample Analysis

All blood samples were analyzed in the same laboratory. The ARCHITECT Phenytoin assay (Abbott Laboratories) is a chemiluminescent microparticle immunoassay (CMIA) that was used in combination with an ARCHITECT i System to quantify the phenytoin concentration in the serum according to the manufacturer's instructions. The ARCHITECT Phenytoin assay has a precision of  $\leq 10\%$  total coefficient of variation (CV).

### Population Pharmacokinetics

Pharmacokinetic parameters estimated using Monolix 4.4 software by applying the stochastic approximation expectation maximization (SAEM) algorithm. Firstly, the base structural model for phenytoin was established. One- and two compartment pharmacokinetic models were compared. Pharmacokinetic parameters were assumed to follow a log-normal distribution. To assess the residual variability, the constant, proportional, and combined error models were tested. The selection criteria for the structural models were reported previously as the following: a) the decrease in the minimum of the objective function value (log-likelihood value); b) the precision of the parameter estimation expressed as the relative standard error (RSE in %) and calculated as the ratio between the standard error and the final parameter estimate; c) physiological plausibility; and d) goodness of fit (GOF) plots that included the observed vs. predicted concentration, residuals plot, and the visual predictive check (VPC). The bioavailability of phenytoin was assumed to be completed and equal 1. The volume of distribution ( $V$ ), the maximal elimination rate ( $V_{max}$ ), and the Michaelis-Menten constant ( $K_m$ ) were estimated for phenytoin.

### Covariate Model

After the proper base model was established, several parameters were tested as potential covariates, including age, gender, body weight, total daily dose (TDD), albumin concentration, total bilirubin concentration, ALT, AST, and the concurrent antiepileptics carbamazepine and valproic acid (VPA). To test for covariates, we used the same approach we reported previously. We started by plotting the individual pharmacokinetic parameters vs. potential covariates to screen for significant correlations. Then, we performed a stepwise regression analysis to test the significant covariates identified in step 1 using the log-likelihood ratio test. If a trend between a covariate and a pharmacokinetic parameter was found, the covariate was considered for inclusion in the base model.

### Model Evaluation

We evaluated the model as reported previously. GOF plots were used as the first indicator of suitability, including the representation of model-based individual predictions (IPRED) and population predictions (PRED) versus the observed concentrations. VPC was constructed using the 10th, 50th, and 90th percentiles of the observed data to evaluate the performance of the final model.

## RESULTS

Table 1: Summary of patient characteristics.

Characteristics	Mean (SD)	Range
Age	41(18.7)	18-84
Gender, % male/%female	70/30	
Weight (Kg)	65.4 (17.7)	25-115
Height (cm)	160.3 (11.1)	125-181
Phenytoin dose (mg)	330.5 (104.5)	50-600
Phenytoin serum concentration (mg/L)	11.2 (10.3)	0.5-37.9
Creatinine clearance (ml/min)	106.7 (56.6)	10-125
Total bilirubin concentration	13.7 (17.5)	1.75-63.4
Albumin concentration	26.5 (6.2)	13.8-41.6
ALT	50.9 (41.1)	6-282
AST	49.5 (38.1)	2-171
Concurrent antiepileptics, n (%)		
Carbamazepine (CBZ)	4 (9.3)	
Valproic acid (VPA)	8 (18.6)	

Table 2: Population pharmacokinetic model estimates for orally administered phenytoin.

Parameter	Population estimate	RSE* (%)
$V$ (L/kg)	0.61	14
$V_{max}$ (mg/kg/day)	6.12	18
$K_m$ (mg/L)	5.33	16
IIV** for $V$ (%)	18	10
IIV** for $V_{max}$ (%)	23	19
IIV** for $K_m$ (%)	25	20
Residual errors		
A	0.15	16
b	0.05	18

\*RSE, relative standard error; \*\*IIV, inter-individual variability expressed as the coefficient of variation,  
 $V_{max} = 6.12 \times (\text{Age}/41)^{-0.16} \times (\text{Body weight}/65.4)^{0.36}$   
 $K_m = 5.33 \times 2.66$  (if co-therapy with VPA)

## RESULTS

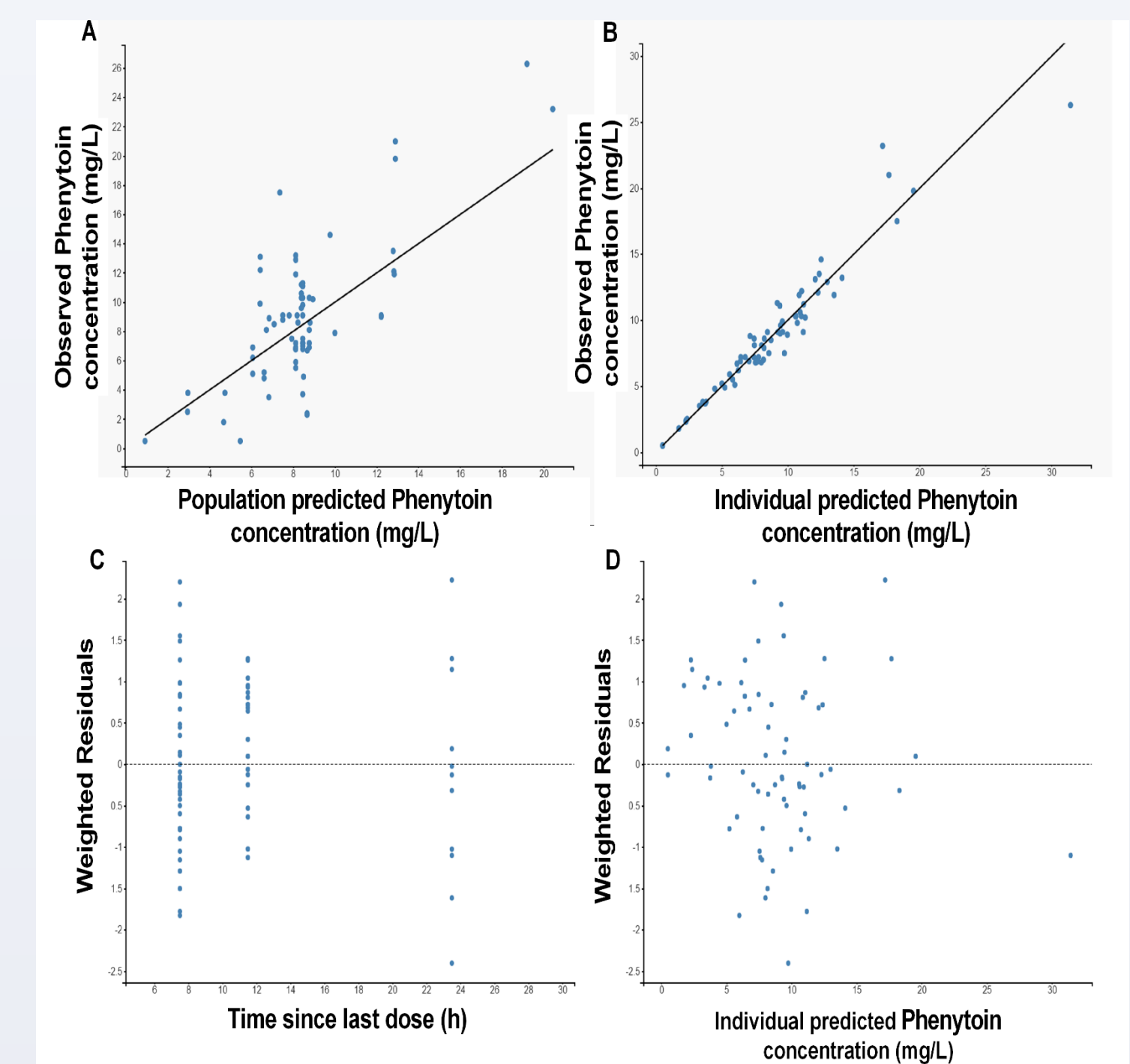


Figure 1. Goodness-of-fit (GOF) plots obtained from the final model for phenytoin. (A) The population predictions of phenytoin vs the observed concentrations. (B) The individual predictions of phenytoin vs the observed concentrations. (C) The weighted residuals versus the time since last dose. (D) The weighted residuals versus the individual predicted concentrations.

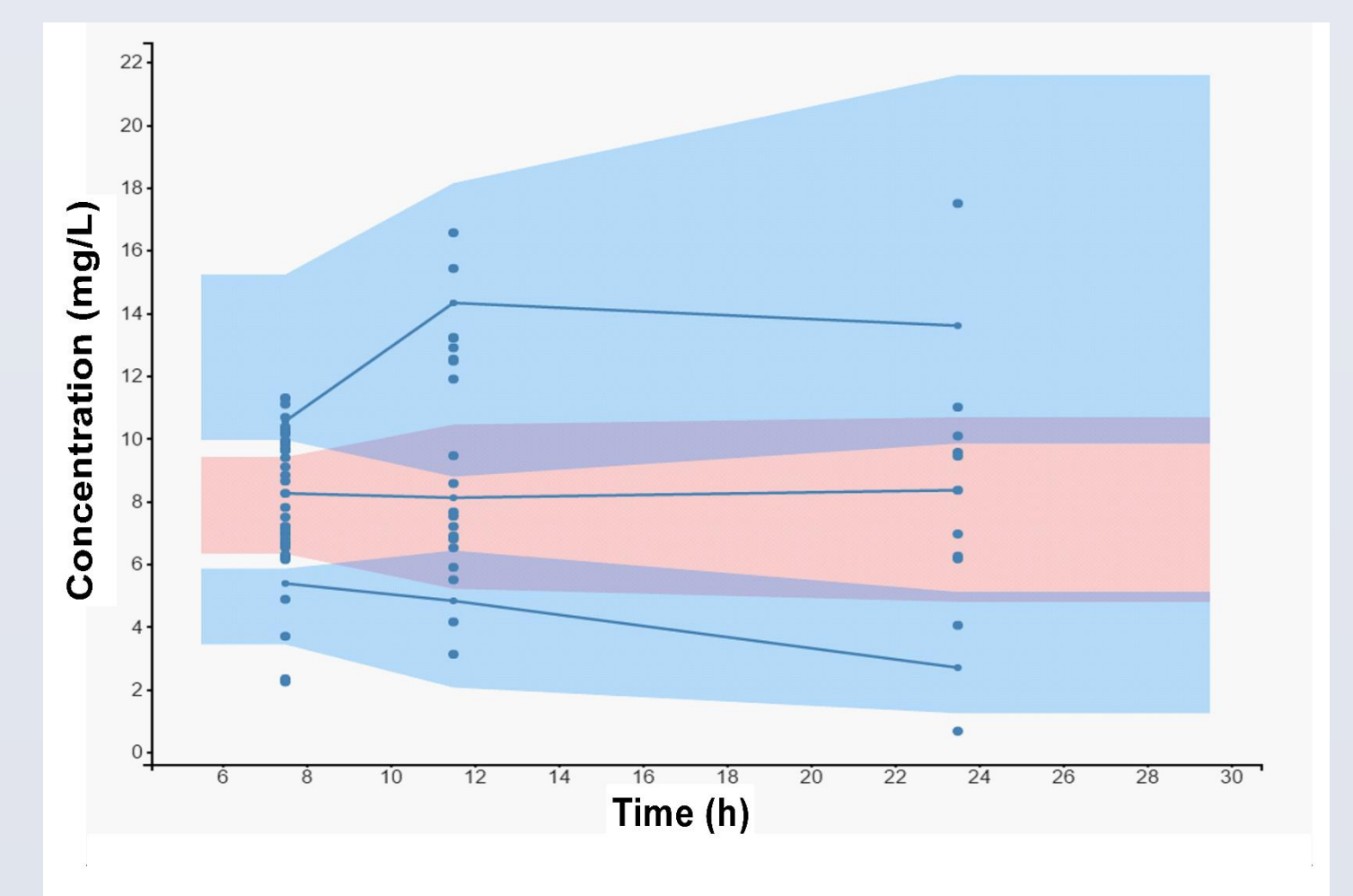


Figure 2. Visual predictive check (VPC) for phenytoin concentration vs time based on 1000 Monte Carlo simulations. The solid green lines represent the 10th, 50th, and 90th percentiles of the observed data. The shaded regions represent the 90% CI around the 10th, 50th, and 90th percentiles of the simulated data.

## CONCLUSIONS

The population pharmacokinetic model of phenytoin in Saudi patients was established and significant covariates of this model were identified. This model detected a significant inter-individual variability between the subjects. Furthermore, our findings showed that patients' age, body weight, and co-therapy with VPA are the most significant covariates affecting  $V_{max}$  and  $K_m$  of phenytoin. Further studies will improve our understanding of the factors that may affect the pharmacokinetics of phenytoin and provide guidance for drug dosage decisions.

## ACKNOWLEDGMENT

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