

POPULATION PHARMACOKINETIC ANALYSIS TO INVESTIGATE THE EFFECT OF ETHNICITY FOR EXTRAPOLATING DATA FROM CAUCASIANS TO KOREANS IN ESLICARBAZEPINE ACETATE THERAPY



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INTRODUCTION

- Eslicarbazepine acetate (ESL) is an antiseizure medication for monotherapy or adjunctive therapy for focal seizures.
- ESL is extensively hydrolyzed primarily in the liver to its major active metabolite, eslicarbazepine (>90%).
- The sensitivity of ESL to ethnic factor was expected to be low considering the known pharmacokinetic (PK), pharmacodynamic (PD) characteristics and PK-PD relationships. However, the PK characteristics were evaluated to extrapolate the efficacy and safety data from Caucasian to Korean patients.

OBJECTIVES

- The study aimed to establish the population PK model of ESL and investigated the impact of ethnicity on PK of ESL.

METHODS

Study Data

- A population PK model was developed from a phase I, randomized, double-blind, placebo-controlled, single and multiple dose-escalation study conducted in healthy adult Korean and Caucasian subjects.
- Korean subjects were assigned to 3 dose groups (400, 800, and 1,600 mg once daily) and Caucasian subjects assigned to 2 dose groups (400 and 1,600 mg once daily) receiving a single dose of ESL and multiple doses once daily for 7 days according to assigned treatment.

PK Model Development

- A total of 1,331 plasma observations from 39 subjects were used to construct the PK model of eslicarbazepine implementing the first-order conditional estimation method with interaction (FOCE-I) method by nonlinear mixed-effect modeling (NONMEM) software (version 7.4).
- As ESL is extensively hydrolyzed to eslicarbazepine and the systemic exposure of eslicarbazepine is more directly related to its efficacy, the PK model of eslicarbazepine was developed.
- The bioavailability and metabolite fraction of eslicarbazepine (F) was included in the PK model.
- The PK structural model were explored including one- and two- compartment models with first- and zero- order. The interindividual variability (IIV) of PK parameters were described as an exponential model.

- Subjects' ethnicity, age, height, weight, and body mass index (BMI) were assessed as potential covariates to investigate the effects on variability in PK parameters. Covariate analysis using the forward-addition and backward-elimination methods was conducted.

Model Evaluation

- The final model was evaluated by assessing goodness-of-fit (GOF) plots, prediction-corrected visual prediction checks (pcVPC), and bootstrapping.
- The bootstrap method was used to create 1,000 datasets by random resampling. The median and 95% confidence interval (CI) were compared with the final PK parameter estimation.

RESULTS

- The PK of eslicarbazepine was well described by a two-compartment model with first-order absorption, and first-order elimination (Figure 1). A combined proportional and additional error model was used for the residual variability (Table 1).
- The population PK parameter estimates (relative standard error, RSE) of first-order absorption rate constant (K_A), apparent clearance (CL/F), apparent volume of distribution of central compartment (V_c/F), apparent peripheral compartment (V_p/F), and apparent inter-compartmental clearance (Q/F) were 0.96 h⁻¹ (16.0%), 2.61 L/h (2.3%), 50.6 L (8.5%), 9.45 L (45.8%), and 4.93 L/h (51.5%), respectively (Table 1). The IIV (coefficient of variation, CV%) on K_A , CL/F and V_c/F improved the PK model estimation, and estimated as 88.8%, 11.6% and 12.7%, respectively (Table 1).
- The effect of ethnicity was investigated as a covariate but no significant impact on the PK parameters was found. No other covariates were also significant to describe the variability of the PK parameters.
- The bootstrap estimates and 95% CI were consistent with the parameter estimates of the final model (Table 1). The model evaluation by GOF plot, and pcVPC suggested that the population PK model was robust and adequate with good precision (Figure 2, Figure 3).

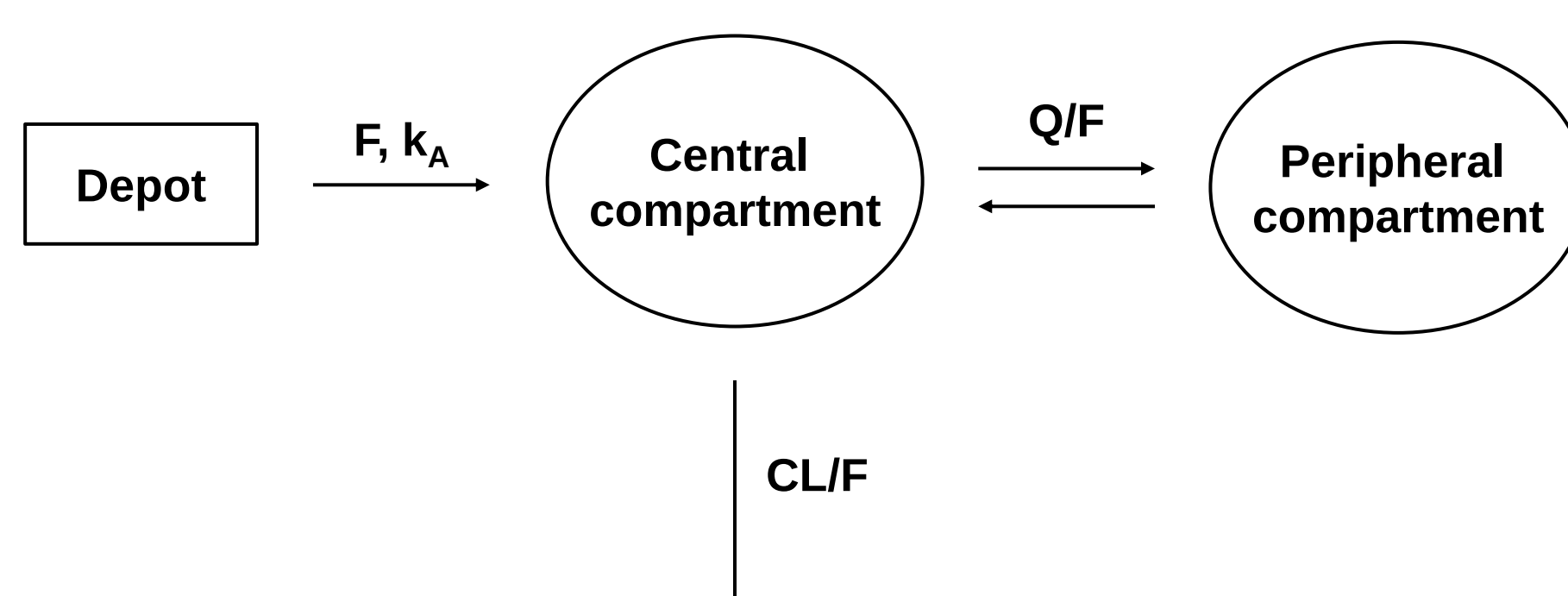


Figure 1. Final pharmacokinetic (PK) model structure of eslicarbazepine.

CL/F, apparent clearance; F, bioavailability and metabolite fraction of eslicarbazepine; k_A , absorption rate constant; Q/F, apparent inter-compartmental clearance

Table 1. Parameter estimation of the final pharmacokinetic (PK) model and bootstrap results

	Final model	Bootstrap
	Estimate (RSE, %)	(n = 1,000) Median (95% CI)
Population parameters		
Absorption rate constant (K_A) (h ⁻¹)	0.96 (16.0)	0.94 (0.67 – 1.26)
Apparent clearance (CL/F) (L/h)	2.61 (2.3)	2.78 (2.50 – 2.73)
Apparent volume of central distribution (V_c/F) (L)	50.6 (8.5)	49.8 (40.8 – 56.9)
Apparent volume of peripheral distribution (V_p/F) (L)	9.45 (45.8)	10.2 (3.1 – 19.0)
Apparent inter-compartmental clearance (Q/F) (L/h)	4.93 (51.5)	5.0 (1.8 – 11.9)
Interindividual variability (CV%)		
ω_{KA} (%)	88.8 (14.2)	86.1 (56.8 – 125.5)
$\omega_{CL/F}$ (%)	11.6 (14.2)	11.3 (8.1 – 14.2)
$\omega_{V_c/F}$ (%)	12.7 (26.8)	12.2 (5.1 – 19.3)
Residual error (CV%)		
Proportional error (%)	19.6 (9.8)	19.6 (15.2 – 23.1)
Additional error (%)	27.0 (25.3)	27.3 (17.0 – 47.1)

Relative standard error (RSE) (%) = (Standard error)/(Estimate) × 100

Abbreviation: CI, confidence interval; CV, coefficient of variation

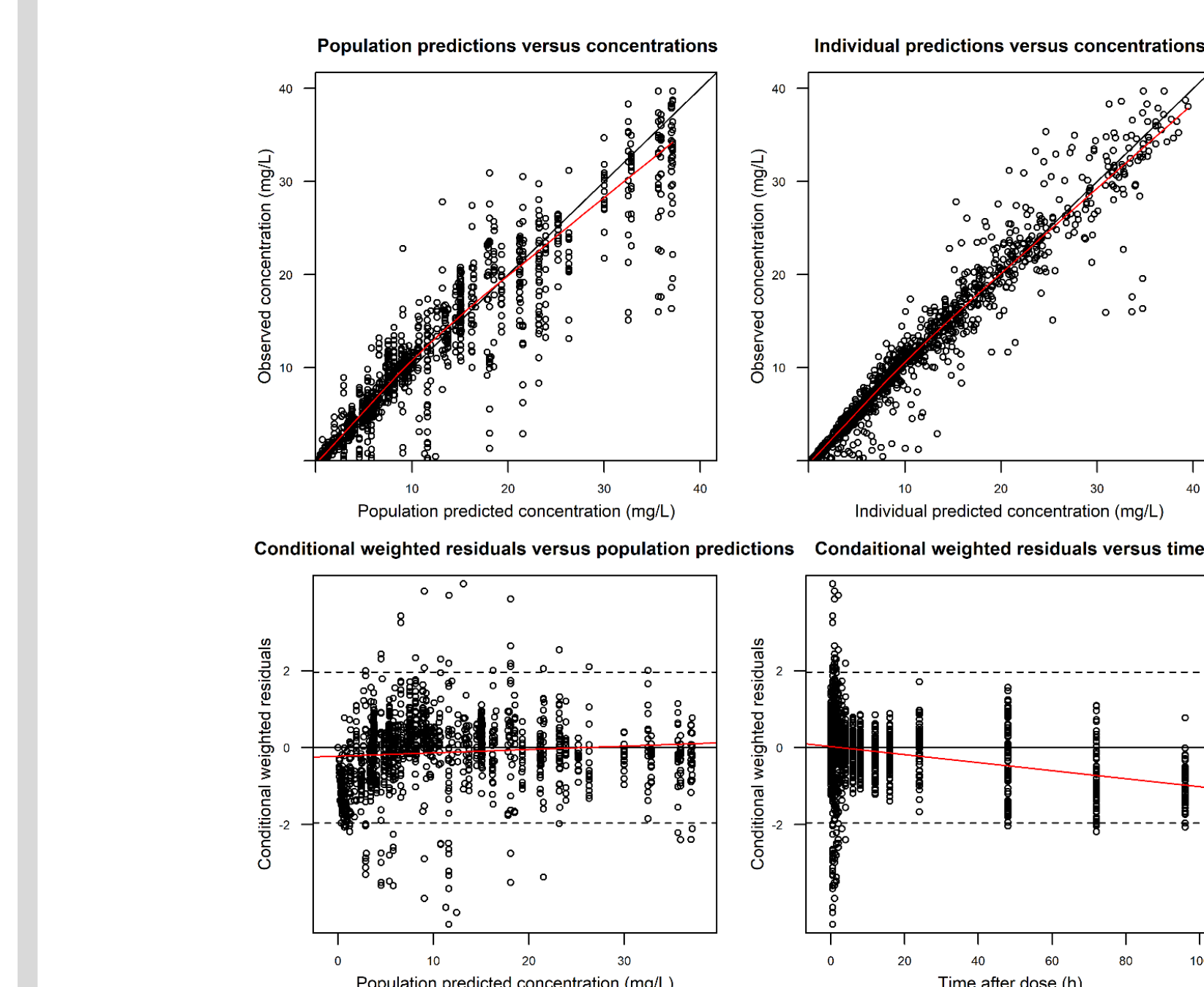


Figure 2. Goodness-of-fit plots of the final pharmacokinetic (PK) model. Open circles indicate observations; solid black lines are the lines of identity; red lines are the line of weighted scatterplot smoothing.

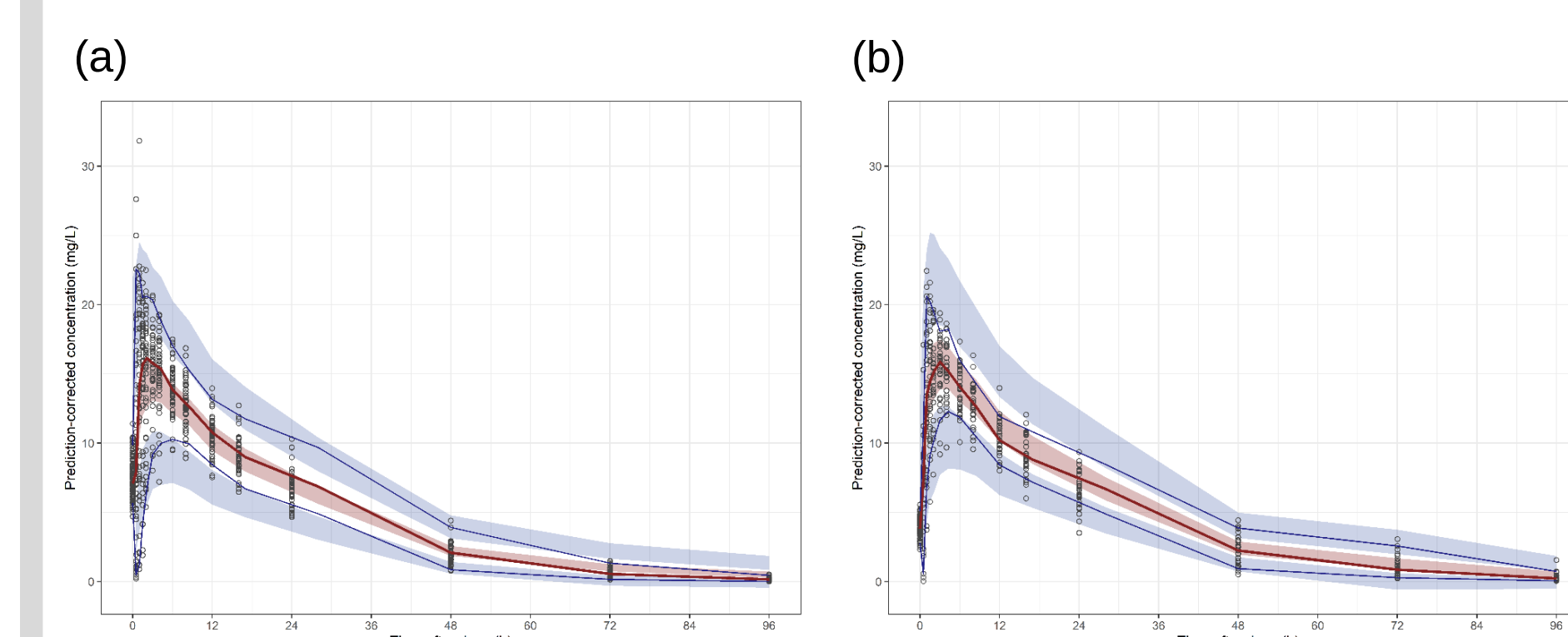


Figure 3. Visual Predictive Checks (VPCs) of the final pharmacokinetic (PK) model in (a) Korean subjects and (b) Caucasian subjects. Open circles indicate observations; solid lines represent the 5th (blue), median (red), and 95th (blue) concentration percentiles; blue and red areas indicate the 90% confidence interval of the simulated concentrations of each percentile.

CONCLUSION

- The population PK model identified that the ethnicity was not a significant factor for describing the variability of the eslicarbazepine PK.

REFERENCES

- [1] Almeida L, et al. The Treatment of Epilepsia (2009), 485-498.
- [2] Bialer M, Soares-da-Silva P. Epilepsia (2012) 53, 935-46.
- [3] Elger C, et al. Epilepsia (2013) 54, 1453-61.
- [4] Galiana GL, et al. Drugs R D (2017) 44, 329-39.
- [5] Trinkka E, et al. Epilepsia (2018) 59, 479-91.