

Population pharmacokinetic/pharmacodynamic modeling of transformed binary effect data of triflusal in healthy Korean male volunteers

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Background

Triflusal (2-acetoxy-4-trifluoromethyl benzoic acid; CAS 322-79-2) is a platelet antiaggregant with structural similarities to salicyclates, but which is not derived from aspirin. After oral administration, triflusal is rapidly absorbed, with a bioavailability of 83 – 100% and is also rapidly deacetylated to its main active metabolite, 2-hydroxy-4-trifluoromethyl benzoic acid (HTB), with a short elimination $t_{1/2}$ of 0.53 ± 0.12 h.

Objective

The main goal of this study is to develop a population pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation of triflusal in healthy Korean male volunteers. The secondary aim was to explore the optimal dosing regimen through the modeling and simulation study.

Method

A randomized, open-label, two-period, multiple-dose, crossover study was conducted in 38 subjects. All eligible subjects received the test (enteric-coated formulation of triflusal) or reference (triflusal) formulation as a single 900 mg loading dose (day1) followed by eight 600 mg/day maintenance doses on days 2 - 9, with a 13-day washout period. Blood samples were drawn at 0 (pre-dose; baseline), 24, 48, 96, 144, 168, 192, 192.5, 193, 194, 196, 199, 202 and 216 h (from day 1 to day 10) after administration of the loading dose. The samples were analyzed by HPLC/MS/MS, to determine the plasma concentrations of HTB, the main active metabolite of triflusal. To determine arachidonic acid-induced platelet aggregation, blood samples were collected at 0 (pre-dose), 24, 48, 96, 144, 168, 192, 196, 202 and 216 h after administration of the loading dose. The platelet aggregation response to arachidonic acid was determined using turbidimetric aggregometry. Platelet aggregation results were expressed as the maximum percentage change in optical density, with platelet-poor plasma used as a reference for 100% light transmission or aggregation. The values of maximum platelet aggregation (MPA) were transformed into binary data as follows: Inhibition of platelet aggregation (IPA) does not occurs (DV=0) if MPA is below 74, and IPA occurs (DV=1) if not as a guideline. A population PK/PD modeling was performed using NONMEM (Ver. 6.2) and a simulated prediction study was performed by the visual predictive check (VPC).

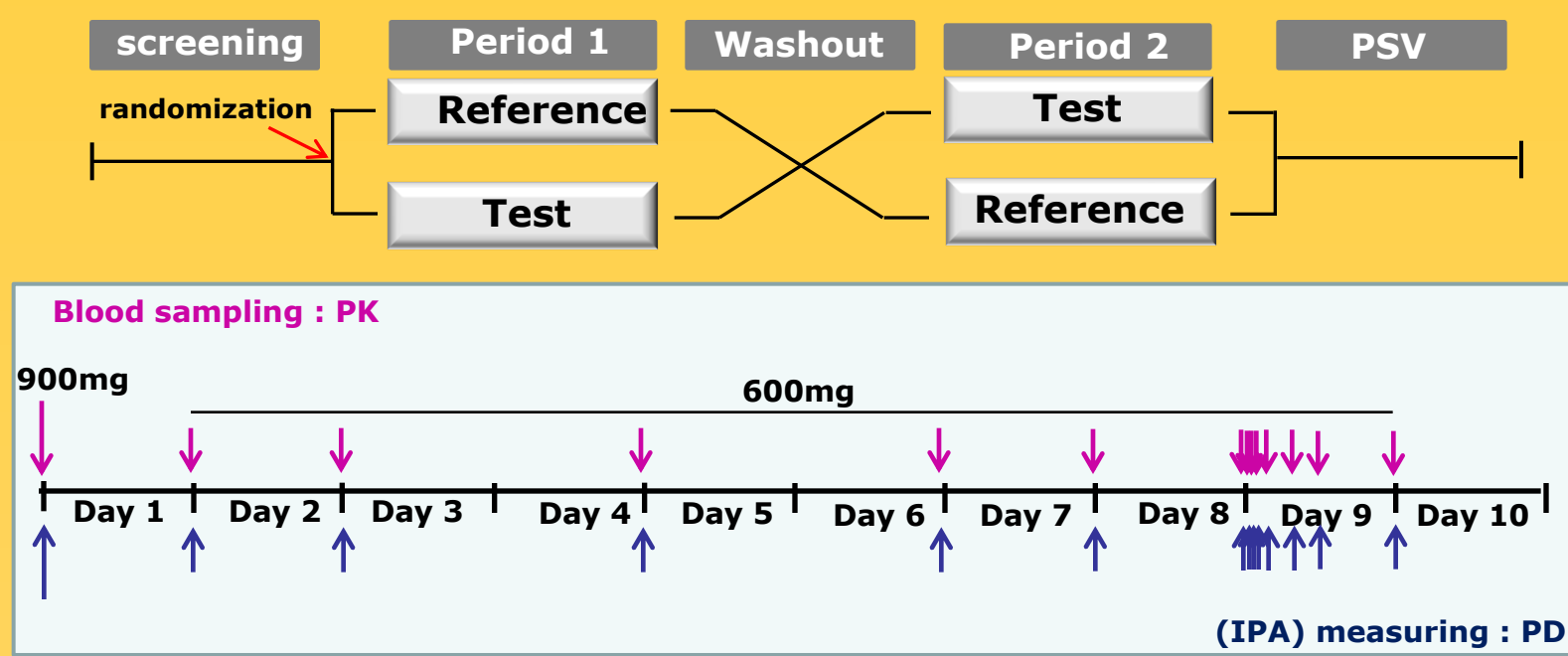


Figure 1. PK/PD Study design

Results

PK

A 1-compartment model with first-order absorption best described the plasma concentrations of HTB. Estimates of the population PK parameter were as follows; CL/F , 0.19 L/h; V/F , 8.31 L; K_a , 0.34 h⁻¹. CLCR and body weight were selected as covariates through Generalized Additive Modeling (GAM). The accuracy and robustness of the final population model were evaluated using a simulation method. The simulation method was conducted by the VPC and the result (Figure 4) exhibited the acceptable predictive performance of the final PK model.

PD

Because the inter-individual variability on each time is too extreme like a yes or no response, some limitation exists even in a well-developed PD model with the quantitative data. Accordingly, a binary data model was used in our study, to check whether or not the effect exists. The model was parameterized using the median effective concentration (EC_{50}) and steepness (γ) of relationship between the concentration and response. The equation of the probability for the response at a certain plasma concentration is

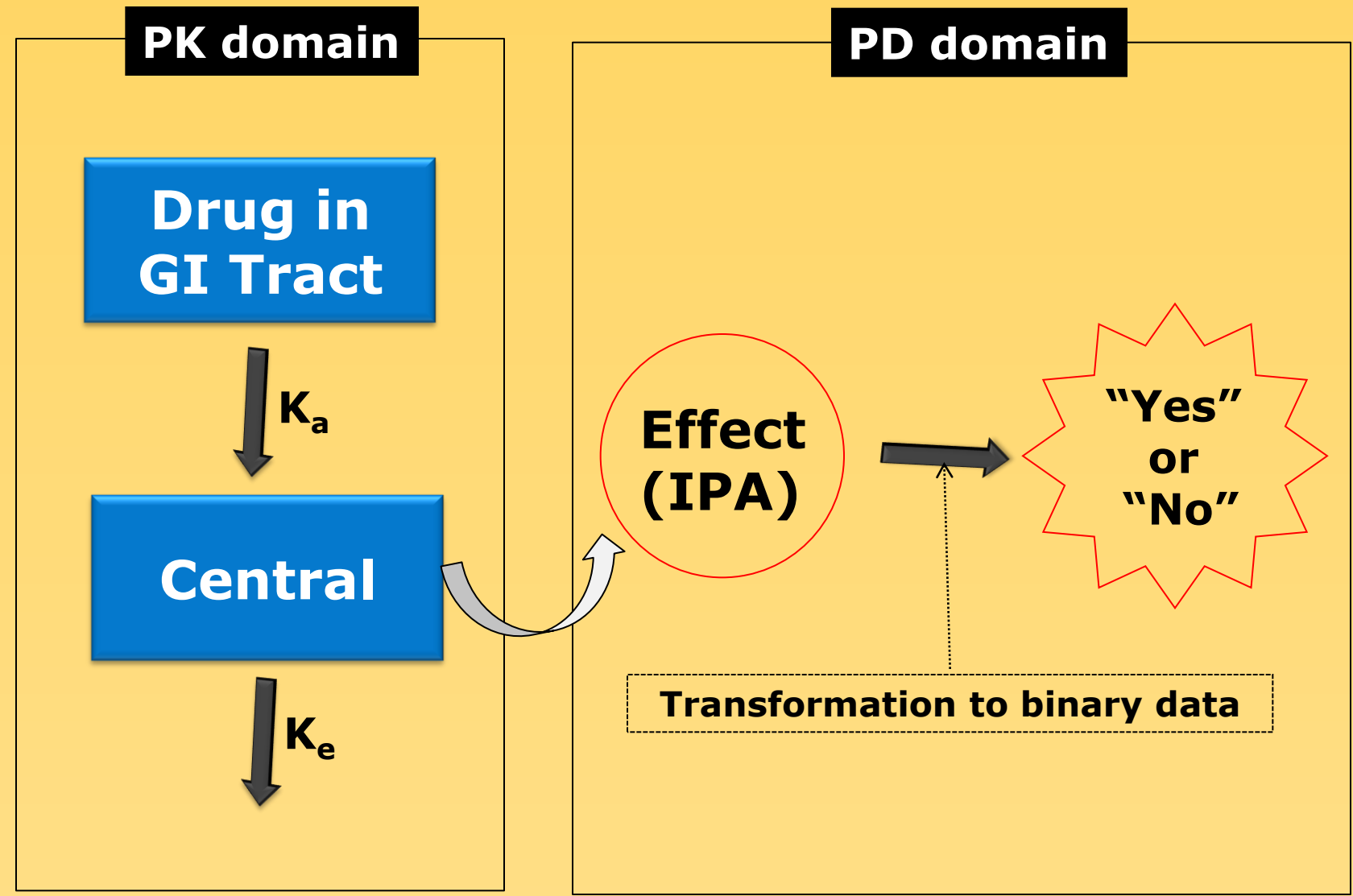
$$\text{Probability} = \frac{C_p^\gamma}{(EC_{50}^\gamma + C_p^\gamma)}$$

The plots of Figure 6, 7 and 8 indicated how well the simulated or predicted output of the PD model matches the measured output.

Demographics

Number of subjects	34
Age (yrs) (range)	Mean±SD (Min - Max) 24.1±1.7 (21-28)
Height (cm) (range)	Mean±SD (Min - Max) 176.1±4.9 (167.1-184.2)
Weight (kg) (range)	Mean±SD (Min - Max) 70.8±9.0 (53.3-89.7)

PK/PD Model



Concentration-Time profiles

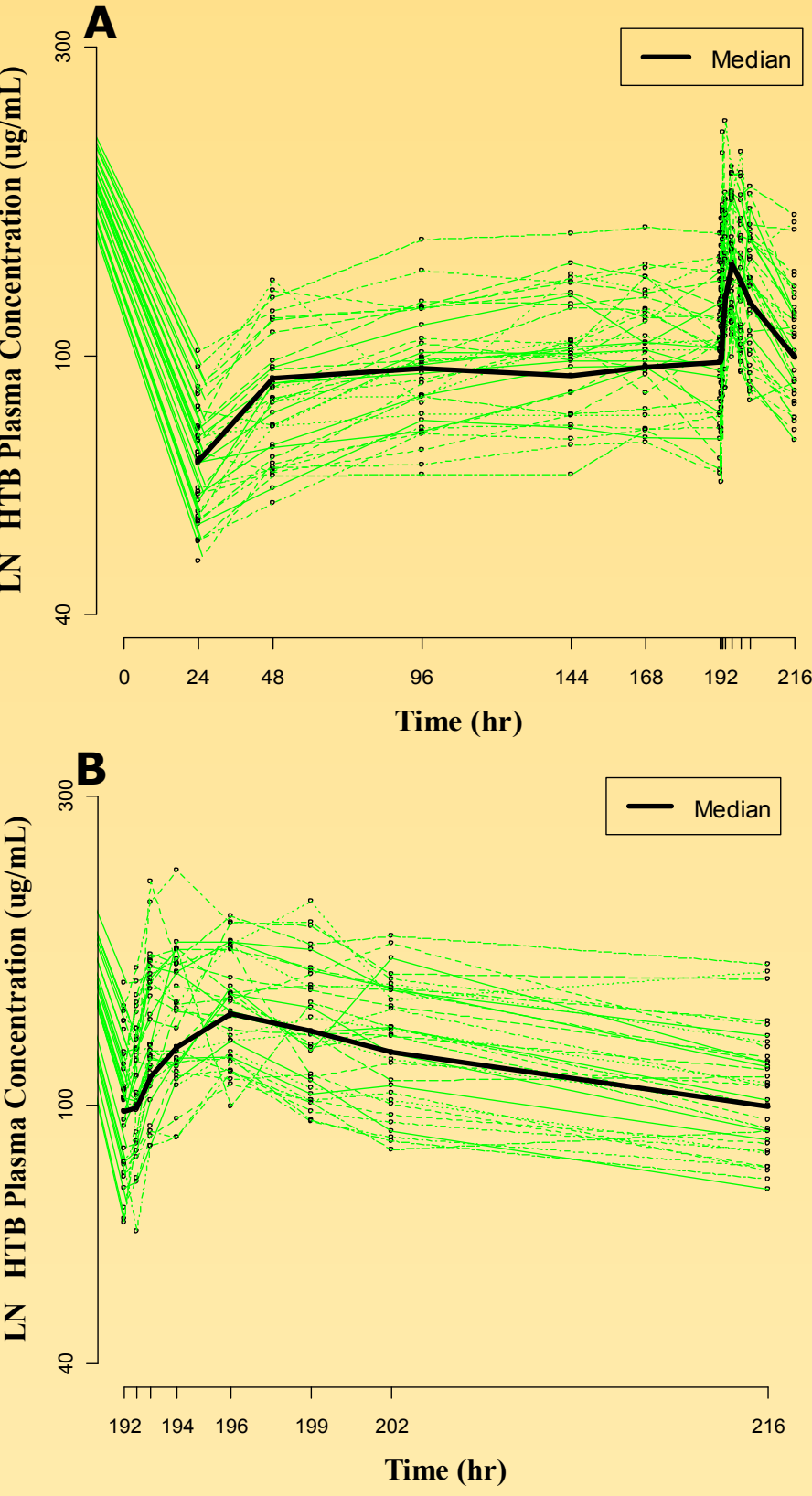


Figure 2. A. Individual and median plasma concentration-time profiles of HTB B. Details of time (192-216h)

PK Basic Goodness-Of-Fit Plot

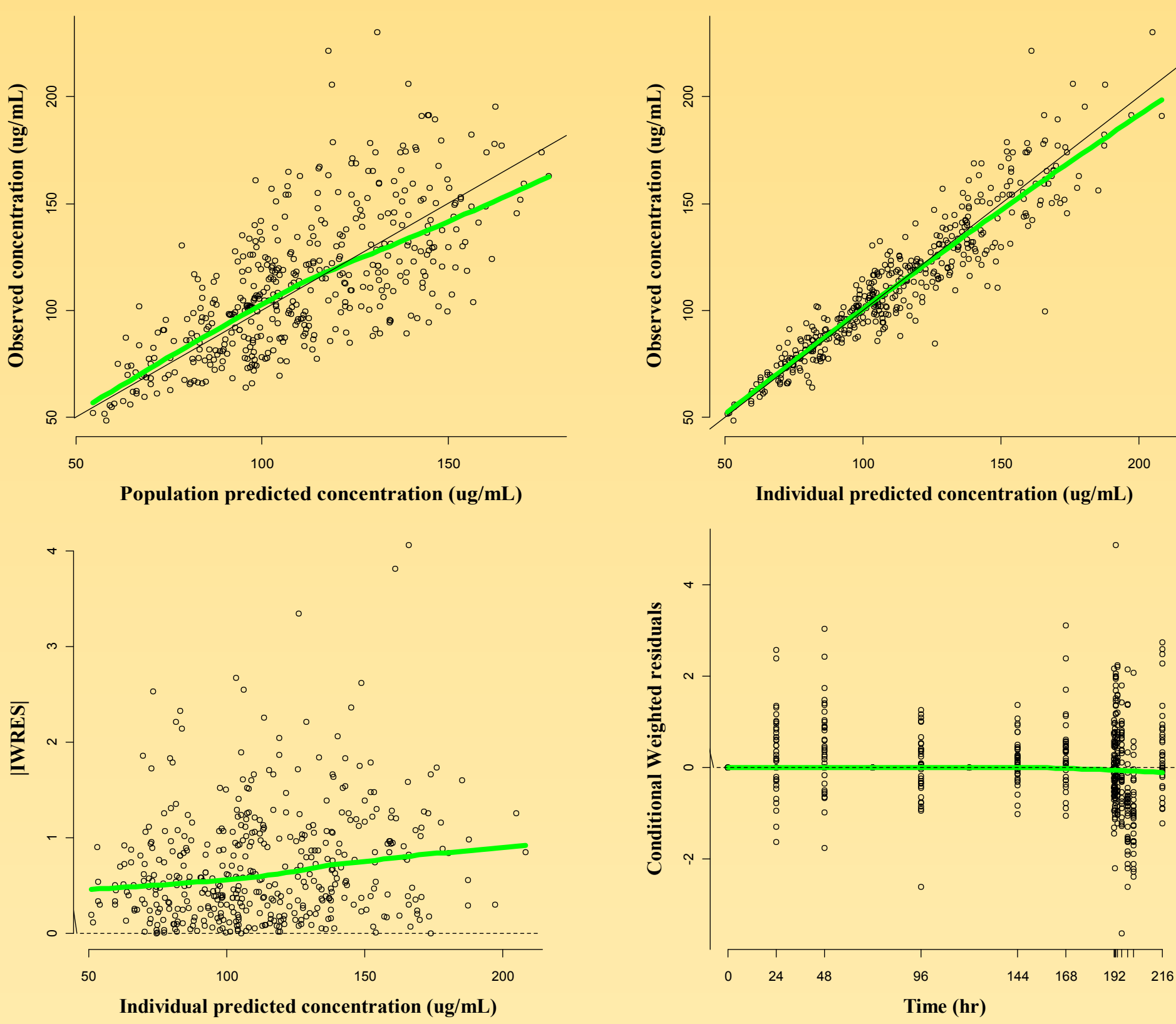


Figure 3. Scatter plots of the final population PK model (circle: observation, solid black line: line of identity, green line: loess regression line)

VPC Plot

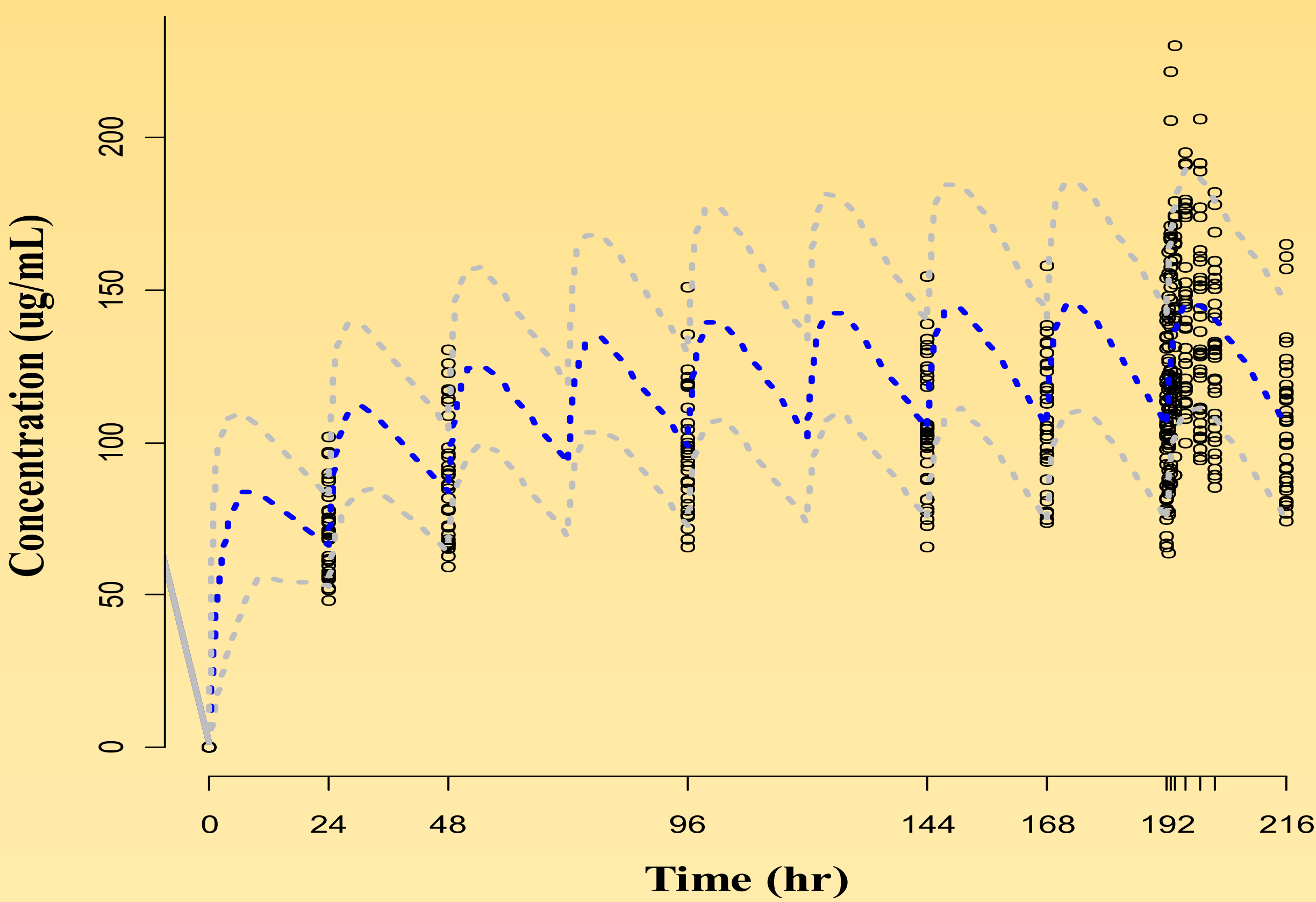


Figure 4. Results of model evaluation using simulated data. The 5th and 95th percentiles (dashed gray line) and the median value (dashed blue line) from the simulated data are plotted against the observed concentration data (circle) according to time.

PA (%) -Time profiles

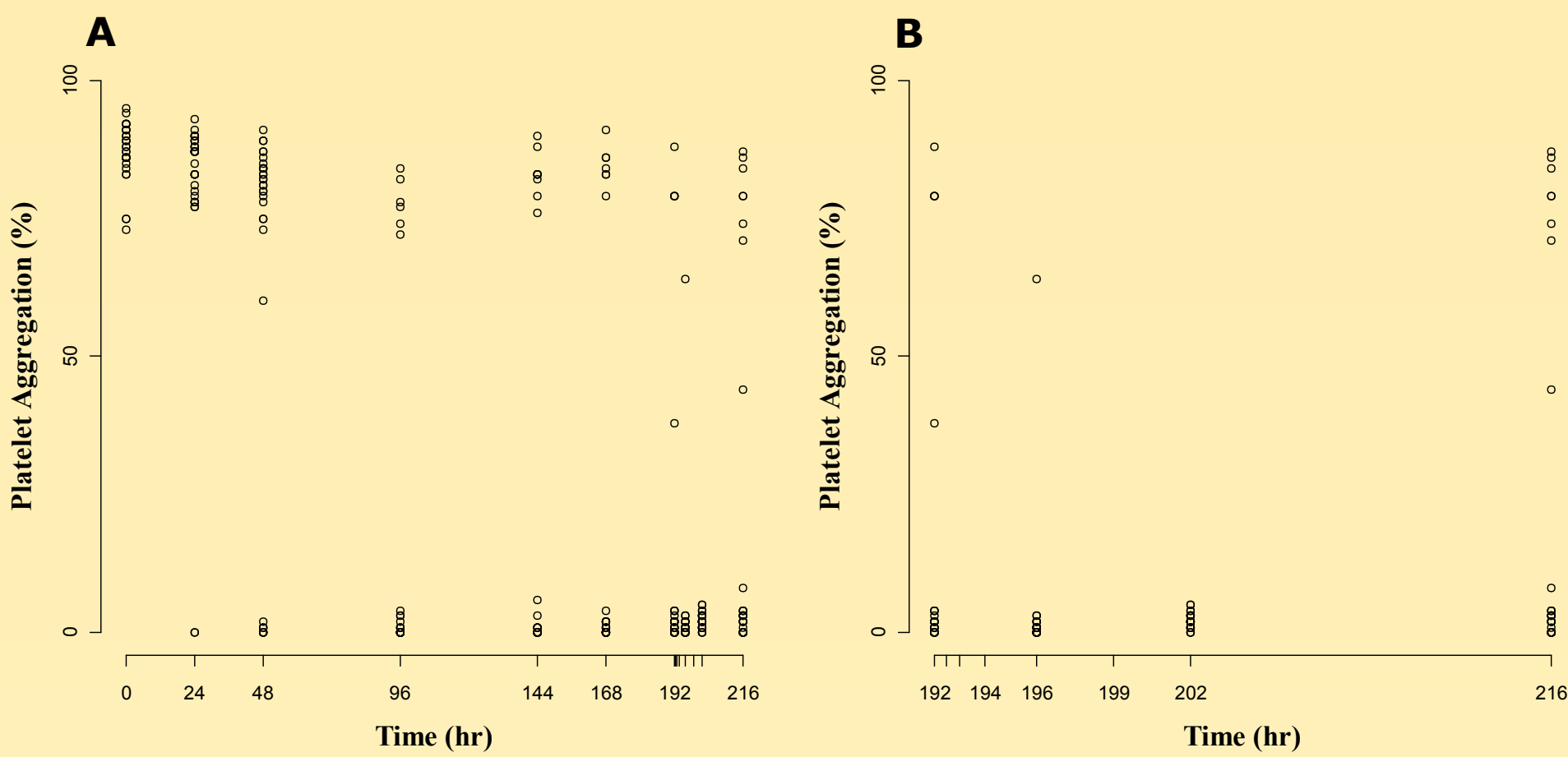


Figure 5. A. Scatter plots of observed PA (%) -time B. Details of time (192-216h)

PD Probability of IPA vs. Time

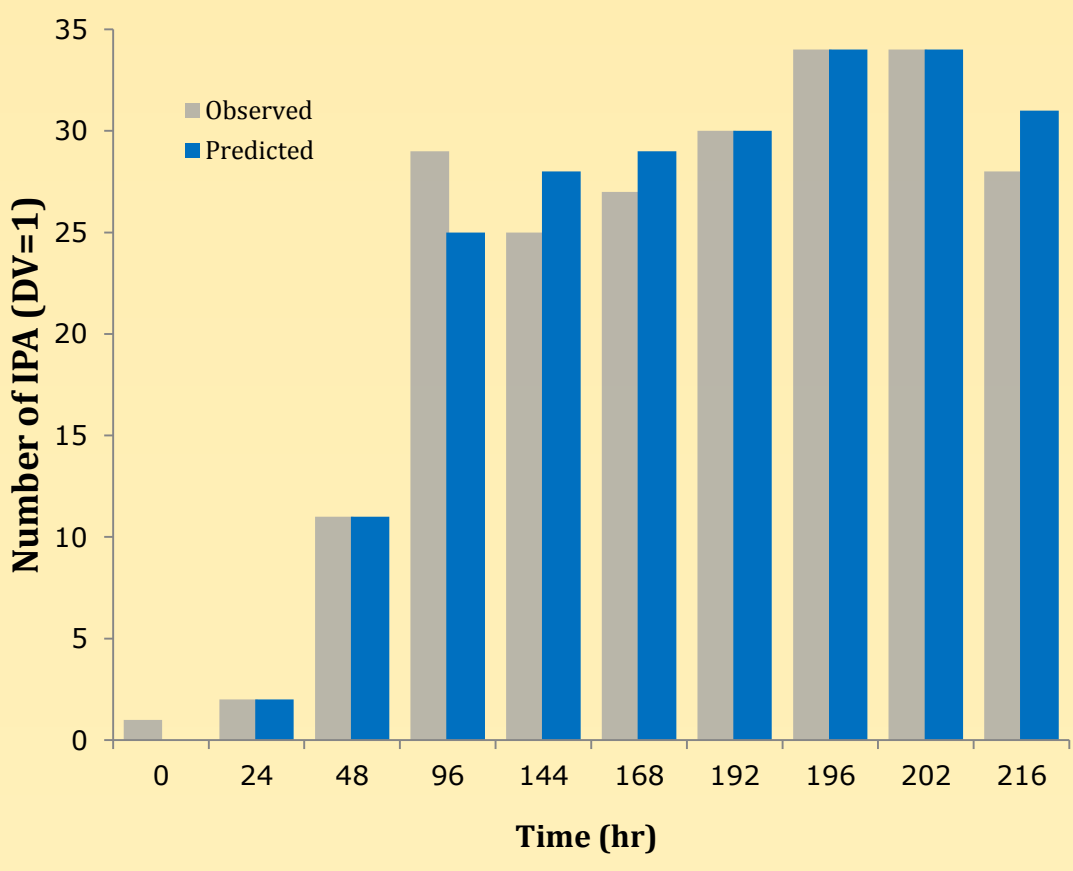


Figure 6. Bar plot for the number of IPA (DV=1, IPA occurred)

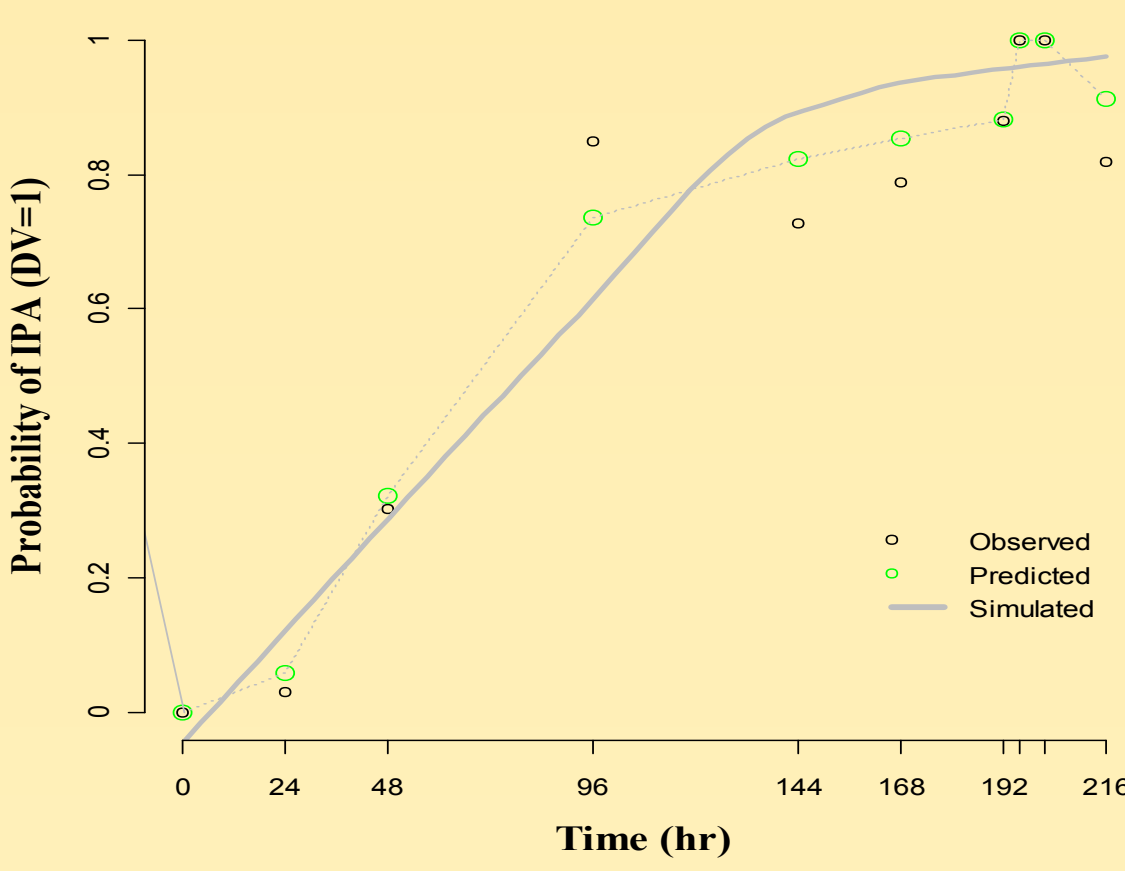


Figure 7. Scatter plots of observed (black circles), predicted (green circles) and simulated (loess regression line for 1000 iterations)

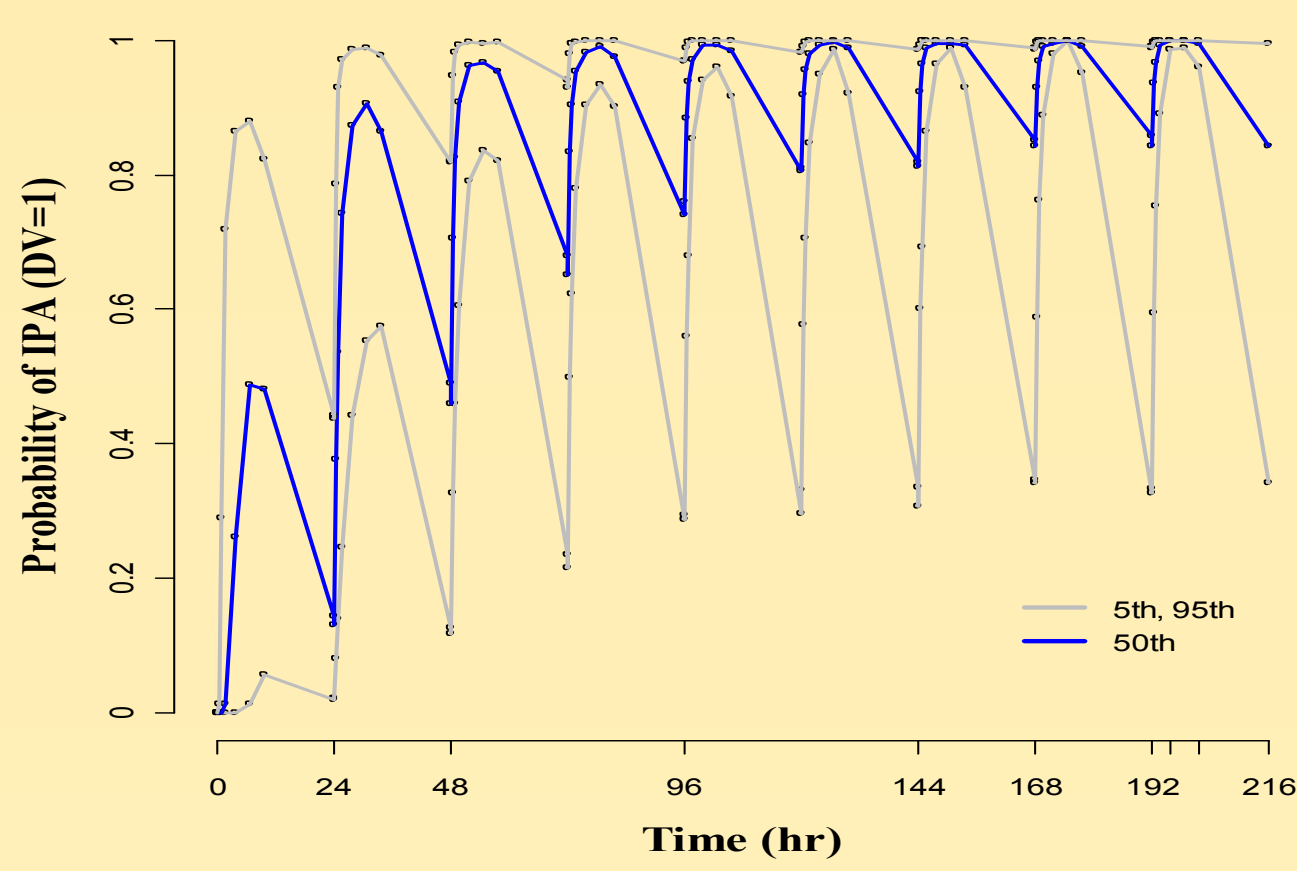


Figure 8. Plot of the simulation results using the 5th, 50th and 95th concentration of the simulated data

Conclusion

A population PK model for triflusal in healthy volunteers was successfully developed and reasonable parameters were obtained. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of triflusal. Some limitation exists in well developing PD model with the quantitative data because the inter-individual variability on each time is too extreme like a yes or no response. It is suggested that PD data be treated as binary data. A current PD model (binary data model) was developed in spite of information loss from the data transformation and it might be clinically useful for similar studies.

References

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