



Application of Different Methodologies to Explain the Pharmacokinetic Variabilities in Pregnant Women: Case Study of Sulindac Usage

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Abstracts

Objectives: Physiological changes during pregnancy are well known and these changes may have various effects on drug pharmacokinetics (PK). The objective of this study was to compare methodologies which could explain pharmacokinetic variabilities of sulindac in pregnant women. **Method:** Blood samples from 68 patients with preterm labor whose gestational age was between 17 and 37 weeks were collected at 1.5 hr, 4 hr, 10 hr after oral administration of 200 mg sulindac. Three methods were applied to explain pharmacokinetic variability in preterm labor patients, (1) dividing gestational age into three trimesters, (2) insertion of covariate related to pregnancy status such as gestational age to PK parameters, (3) apply gestational age functions. Pharmacokinetics of sulindac and variability was evaluated using the nonlinear-mixed-effect modeling program (NONMEM® 7.3.0). Goodness of fit plots and visual predictive checks were conducted to verify model and to confirm concordance with observed data. **Results:** Population pharmacokinetic parameters were estimated based on 357 plasma samples. Data were adequately described by a one-compartment model. V_d/F and CL/F of sulindac was estimated to be 47.6 L and 6.09 L/hr, respectively. The third method which apply gestational age functions described the observed variability well in PK data from preterm labor patients. **Conclusion:** Population pharmacokinetic models were developed which can adequately describe the plasma concentrations of sulindac in patients with preterm labor. The gestational age function was a good tool to predict pharmacokinetics in pregnant women. We plan to expand this model to include an active and an inactive metabolites of sulindac. This methodology appears to be promising, therefore its application in other drugs used in pregnancy should be further explored.

1. Introduction

Sulindac have been used as a tocolytic agents (anti-contraction medication) in preterm labor patients. The physiological changes during pregnancy are well known to have various effect on drug pharmacokinetics. Therefore, we have investigated 3 ways to explain the pharmacokinetic of pregnant women and compared each of them.

2. Methods

(1) Patients demographics

- We had 68 preterm labor patients data. Data were collected after 1.5, 4, 10 hr of administration. Key demographics are showed in Table 1.

Table 1. Demographics of preterm labor patients

Characteristics	Mean±SD	Range
Number of paients	68	-
Number of observation	357	-
Age (yr)	32.6 ± 4.3	20 ~ 41
Body weight (kg)	60.9±9.8	45 ~ 92
Gestational age at delivery (weeks)	34.2±6.1	16.3 ~ 41.3

(2) Base models

- Base model was referred from Alexander et al. which is sulindac model for healthy subjects.

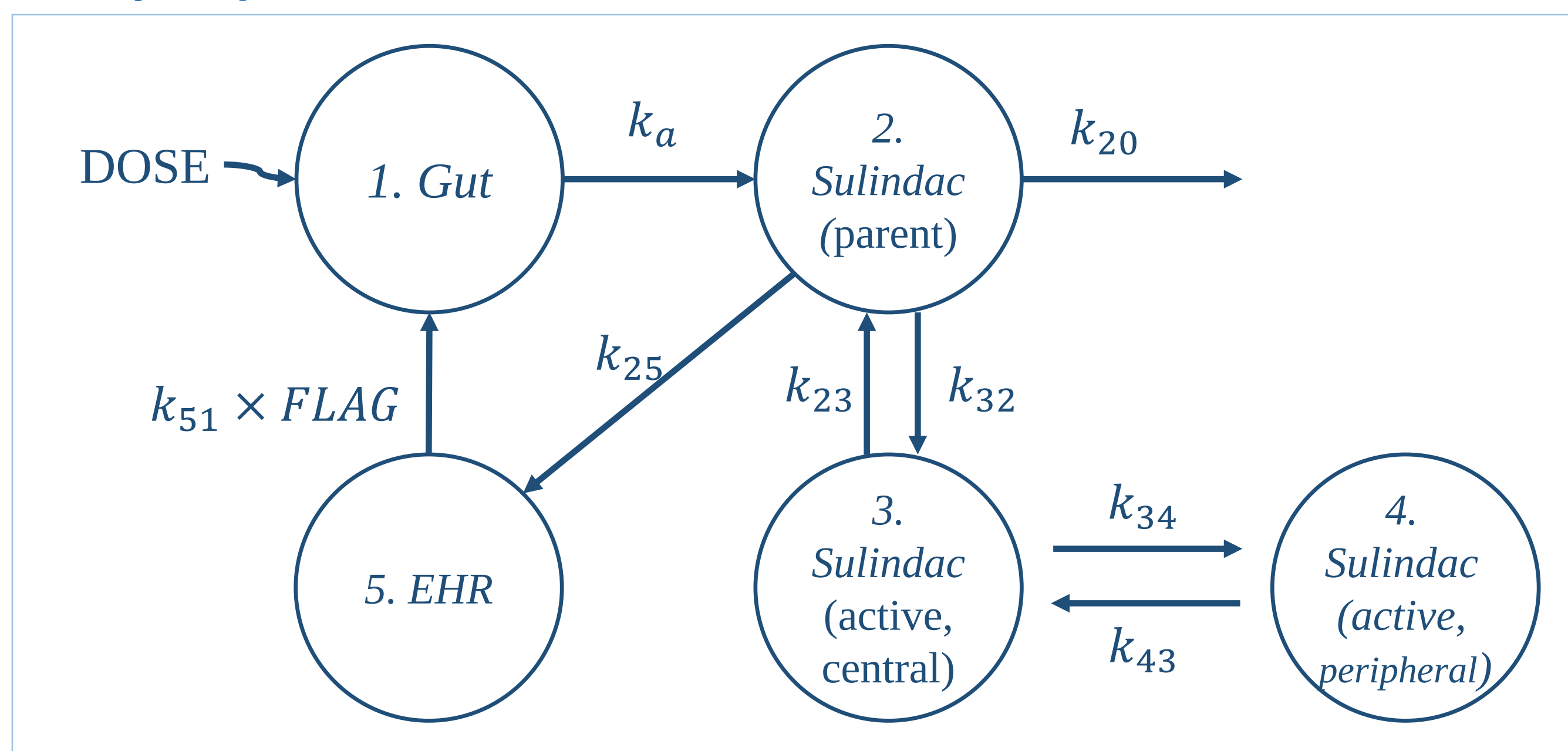


Figure 1. Model scheme of sulindac with healthy subjects

(3) Applicated methods

- During pregnancy, physiological conditions such as cardiovascular, hematologic, metabolic, renal and respiratory changes which could affect pharmacokinetic of drugs
- We assumed that pregnancy could affect eliminate rate constant and volume of distribution of drugs because increase in body weight during pregnancy could affect V_d and other physiologic conditions could decrease or increase eliminate rate constant.

1) Allometric scaling

- While pregnant weight are significant increased. Therefore, we could applicate allometric concepts in pregnancy model

$$\text{Allometric scaling, } Par_{ind} = Par_{pop} \times \left(\frac{WT}{70}\right)^{\theta_1}$$

2) Covariate methods

① Categorization of gestational age

- The pregnancy period were categorised into three trimester, 1~13 weeks / 13 ~ 26 weeks / 26 ~ 40 weeks, each of which is marked by specific fetal development.

In trimester 2 (13 ~ 26 weeks)	$Par_{ind} = Par_{pop} \times \theta_1$
In trimester 3 (after 26 weeks)	$Par_{ind} = Par_{pop} \times \theta_2$

② Gestational age as a continuous covariate

- We modeled gestational age as a continuous covariate in 3 major equations, linear form, exponential form, power form.

Linear form	$Par_{ind} = Par_{pop} \times \left(1 + \theta_1 \times \left(\frac{GA}{\bar{GA}}\right)\right)$
Exponential form	$Par_{ind} = Par_{pop} \times e^{\theta_1 \times \left(\frac{GA}{\bar{GA}}\right)}$
Power form	$Par_{ind} = Par_{pop} \times \left(\frac{GA}{\bar{GA}}\right)^{\theta_1}$

3) Equation insertion

- Following the pregnancy period, physiology can be changed in specific pattern such as hyperbolic plots. So, we tried to model the gestation age as a sigmoidal equation as:

$$Par_{ind} = Par_{pop} \times \left(\frac{\theta_1 \times GA}{\theta_2 + GA}\right)$$

3. Results

(1) Delta OFV comparison

- OFV of each models are show below. In elimination rate constant parameter, GA as covariate with sigmoidal equation and in volume of central compartment parameter, allometric scaling method which considered weight showed lowest value of OFV

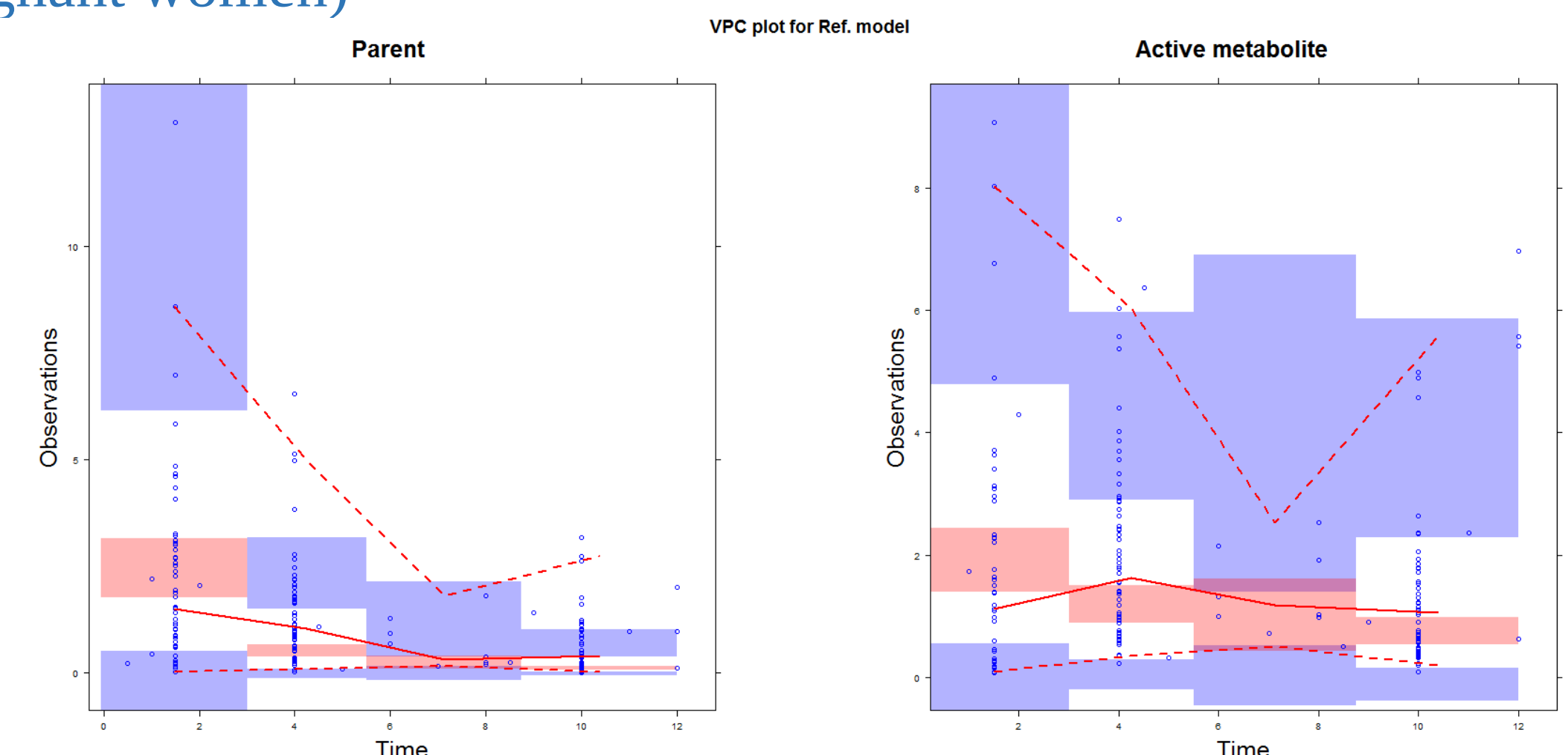
Table 1. Objective function value comparison

Model	OFV	ΔOFV	Model	OFV	ΔOFV
Base model	589.035		Base model	589.035	
Applicate to K20 parameter			Applicate to Vc parameter		
Allometric scaling	584.035	-5	<u>Allometric scaling</u>	<u>581.856</u>	<u>-7.17</u>
Covariate			Covariate		
Categorical	577.172	-11.8	Categorical	588.964	-0.07
Linear form	566.162	-22.8	Linear form	585.141	-3.89
Exponential form	565.712	-23.3	Exponential form	585.066	-3.96
Power form	587.838	-1.19	Power form	587.612	-1.42
<u>Equation</u>	<u>563.507</u>	<u>-25.5</u>	Equation	582.607	-6.42

(2) VPC results

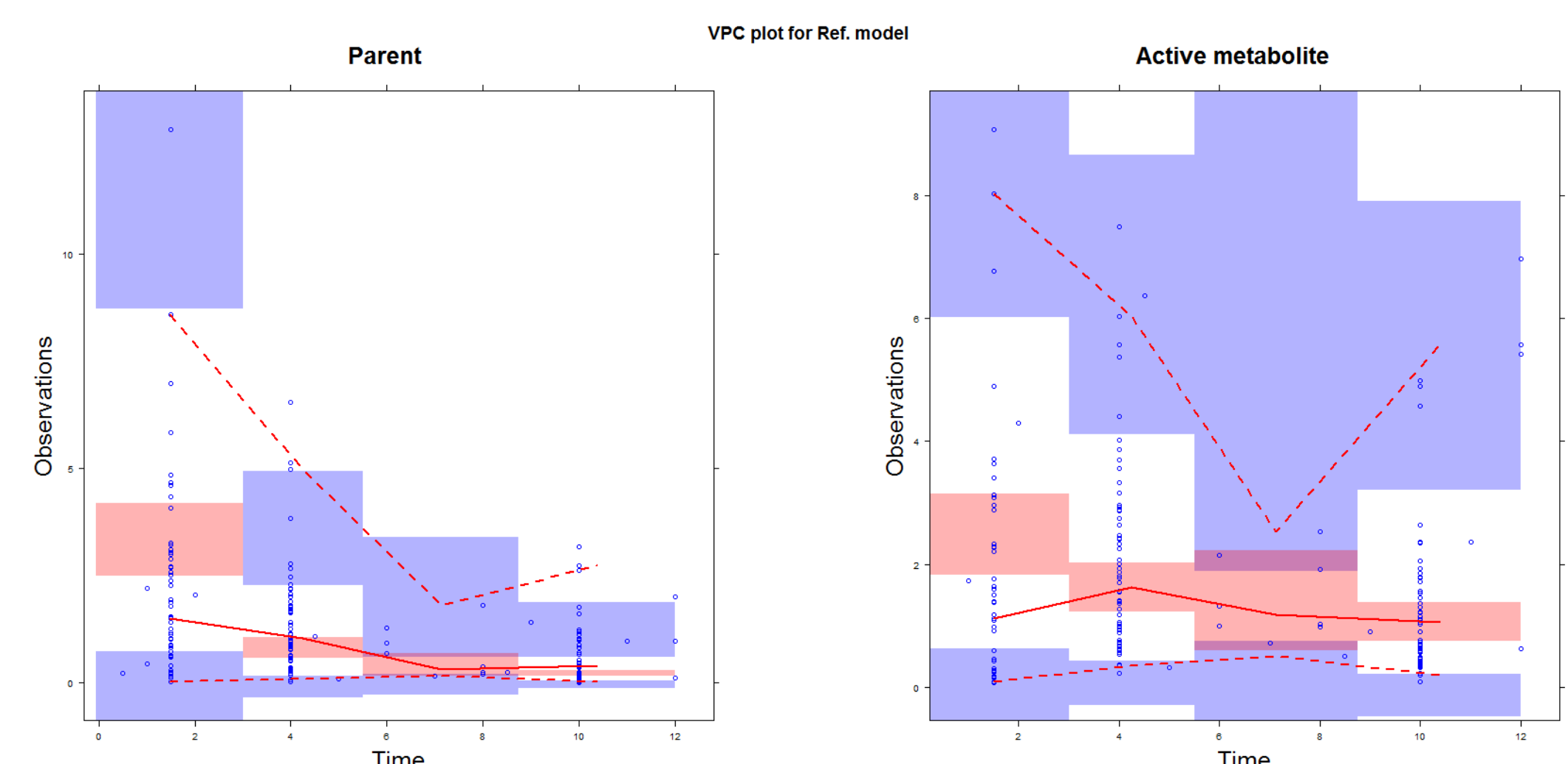
1) Base model results

- VPC from base model are showed in following figure. Model was not well-fitted because the model is for healthy subjects while observations are patients (pregnant women)



2) Final model results

- VPC from final model which considered GA as covariate with sigmoidal equation on K_{20} and allometric function on V_c is shown below. Compared to VPC from base model, we can observe the better fitting of the model prediction and observed data.



4. Discussion and Conclusion

- We applied 3 different methods to explain pharmacokinetic variability in pregnant women.
- Applicating equation of GA to K_{20} and allometric function to V_c decreased OFV significantly.
- During pregnancy physiological changes the clearance gradually and maternal weight changes the volume of distribution.
- In this study, we found a clue that could build a methodological approaches to explain pharmacokinetic variability of special population (pregnant women)

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