Pharmacokinetic model of Primaquine (Anti-malarial drug)

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Contents

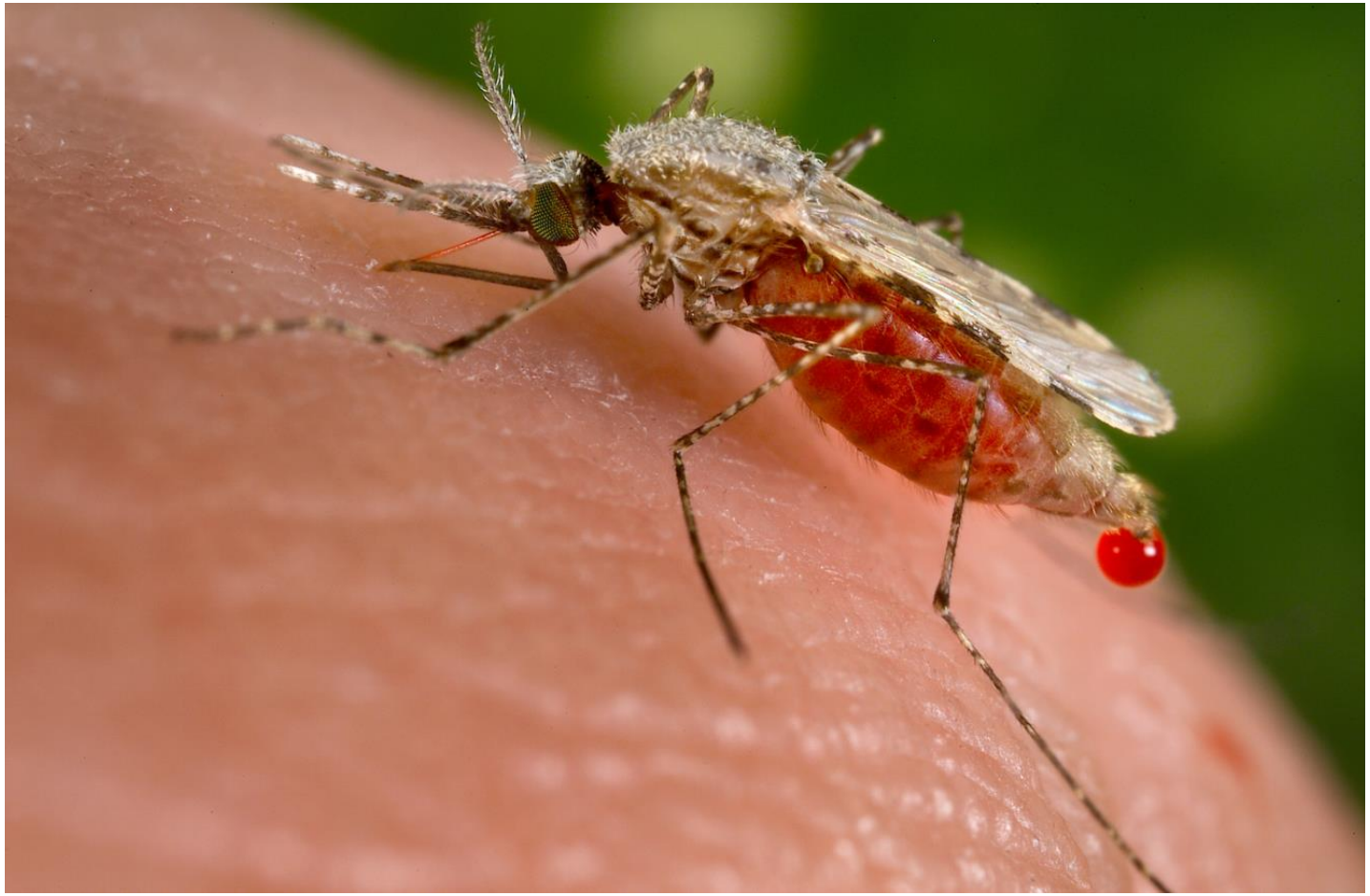
- Introduction
- Objective of the work
- Methods
- Results
- Discussion & conclusion
- Further studies

Introduction

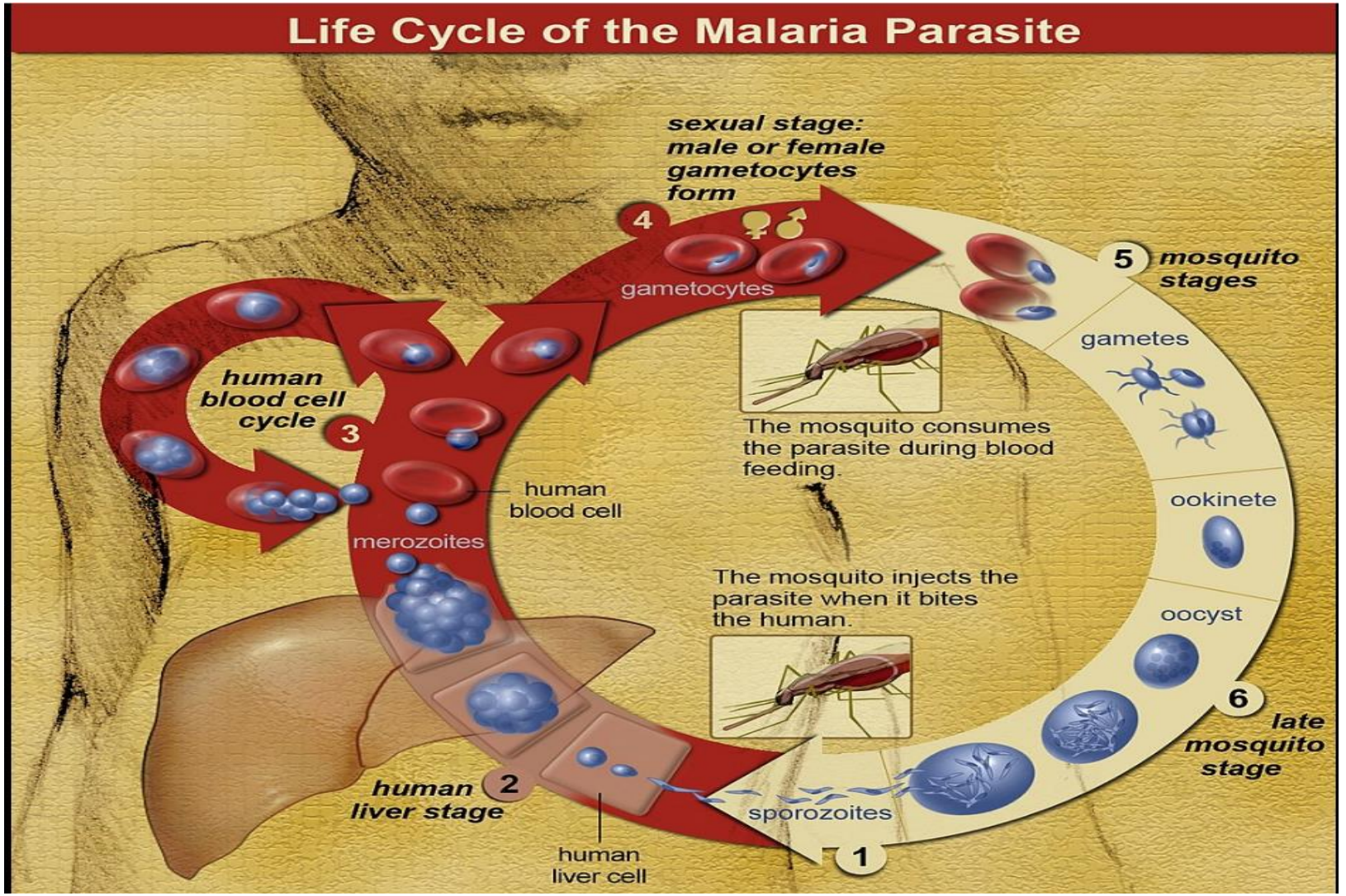
- Malaria
  - Plasmodium parasite transmitted by infected female Anopheles mosquito.
  - Malariogenic : P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi
- Symptoms

- Typically begin 8–25 days following infection
  - headache, fever, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobinuria, convulsions
  - cerebral malaria (P. falciparum)
  - Fever: tertian fever (P. vivax, P. ovale), quartian fever (P. malariae)

Introduction

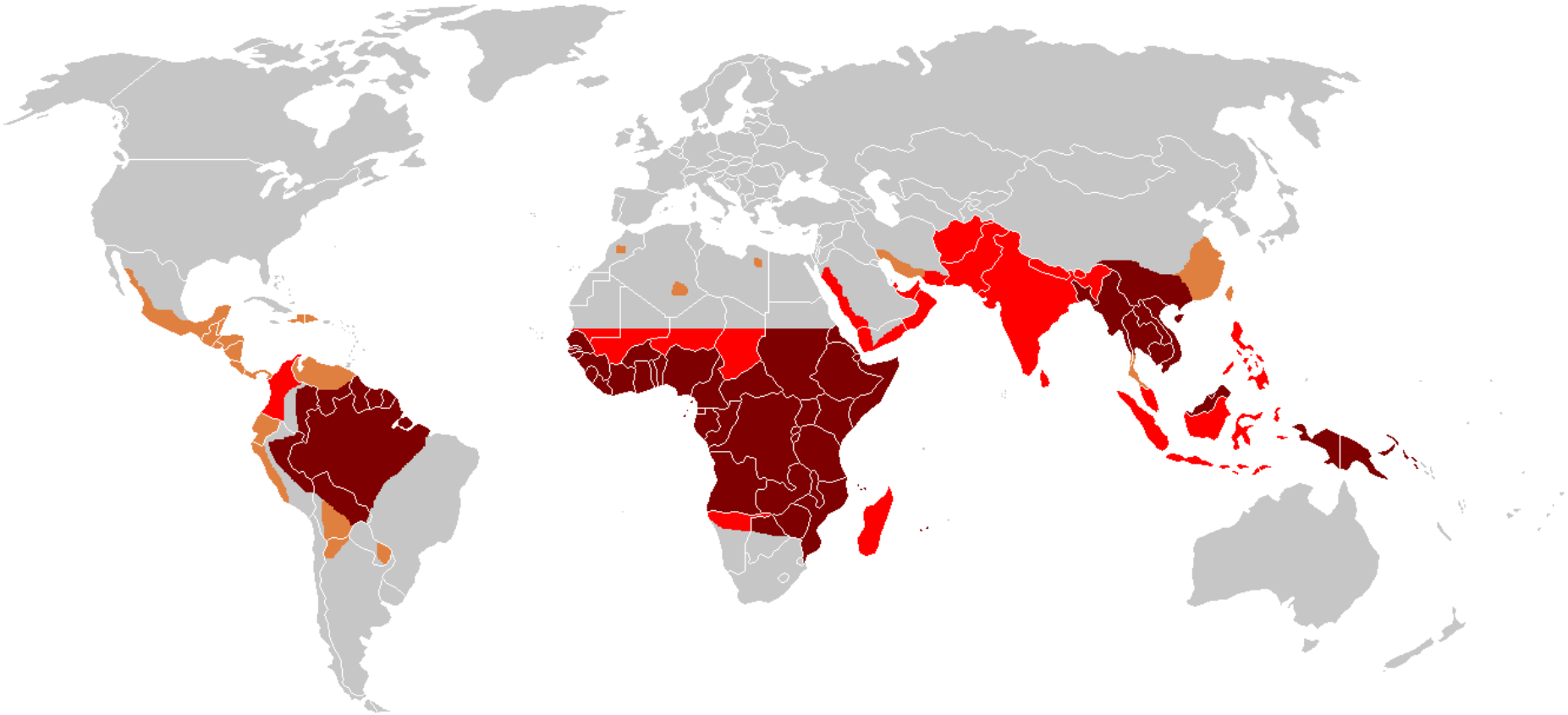


Introduction



Introduction

Endemic areas



Introduction

Epidemiology

Globally,
- over 25 billion people are in malaria endemic region
  -3 billion incidences of infection
  - responsible for over 3 million deaths per year

In South Korea,
- Over 4000 new cases reported in the year of 1998-2000
- declined to 2000 cases in the year of 2006~2007.
- In recent years, there are 500~600 new cases of infections annually.

Introduction

> Treatment
For radical cure : 3 days of hydroxychloroquine overlapped with 15mg of primaquine for 14days

Primaquine (PQ) (8-amino-quinolone):
- for p.vivax and p.ovale treatment, approved by FDA in 1952
- Eliminates hypnozoites, the dormant liver form of the parasite
-kill gametocytes (stage V) of *P. falciparum* and *P. vivax* in blood;
-it also kills asexual trophozoites of *P. vivax* in blood
-Clinical effects are related to exposure of PQ

Introduction

Pharmacokinetic characteristics from literatures

- Absolute bioavailability : 0.96 (oral)
- Half life : 3.7-9.6h
- **Metabolism** :

Mostly metabolized in liver (urine : 0. 5-2.4%)

Main pathways :

a) CYP2D6 - redox cycle, oxidative stress that has treatment and side effect

b) Monoamineoxidase (MAO) - carboxyprimaquine(cPQ)

Controversial role of carboxyprimaquine : Recent findings of hydroxylation pathways in cPQ metabolism

Objective of this study

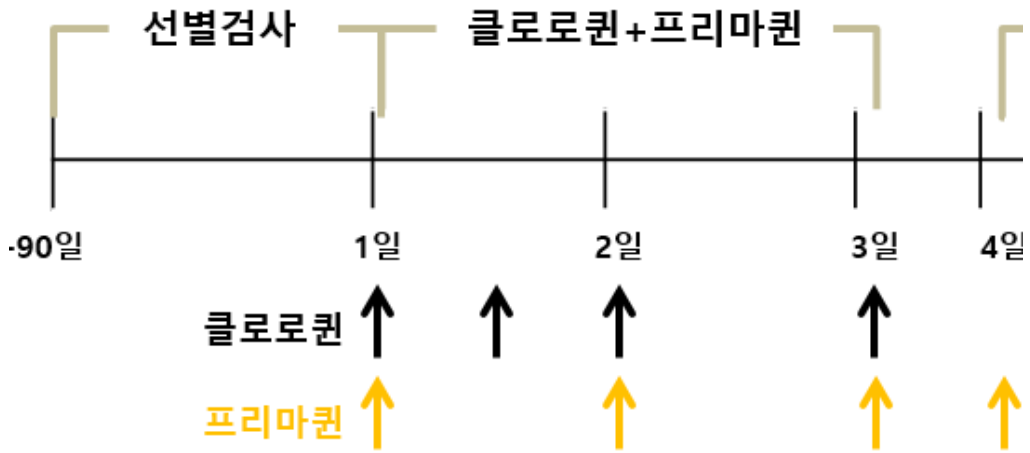
- Develop pharmacokinetic model in Korean population

- Project initiated by KCDC (Korea centers for disease control and prevention)
- investigate pharmacokinetic characteristics of primaquine and its metabolite, carboxy-primaquine in Korean population to be used as a basis of optimal dosing regimen design
- evaluate pk differences in the over weighted group(BMI > 25) comparing to the group with normal body weight

Methods (study design)

Data were acquired from a prospective, open label, parallel designed clinical trial conducted in 24 healthy subjects who received primaquine (PQ) 15mg QD for 4 days co-administered with chloroquine during the first 3 days.

Blood samples were taken at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24h after the last dose.



Methods (Data)

- Total N = 24
- Male = 24 (BMI<25 : 12 , BMI>25 : 12)

Demographics	Min	Median	Mean	Max
AGE	19	26.5	27.8	47
BWT (kg)	56.1	77.5	75.5	95.8
HT (cm)	165.7	173.9	174.2	184.6
BMI (kg/m2)	18	25.1	24.8	31.2

- Activity score (AS) of CYP2D6

	0	0.5	1	1.5	2	2.5
AS	0	1	6	12	5	0

Methods (model)

- Blood concentrations were used as dependent variable in this modeling

- Flow and volume parameters were allometrically scaled to body weight of 70kg. The exponents of the allometric models were fixed at 0.75 and 1 for flow and volume parameters, respectively.

- Primaquine (PQ) and carboxy-primaquine (cPQ) fitting was done simultaneously.

Methods (model)

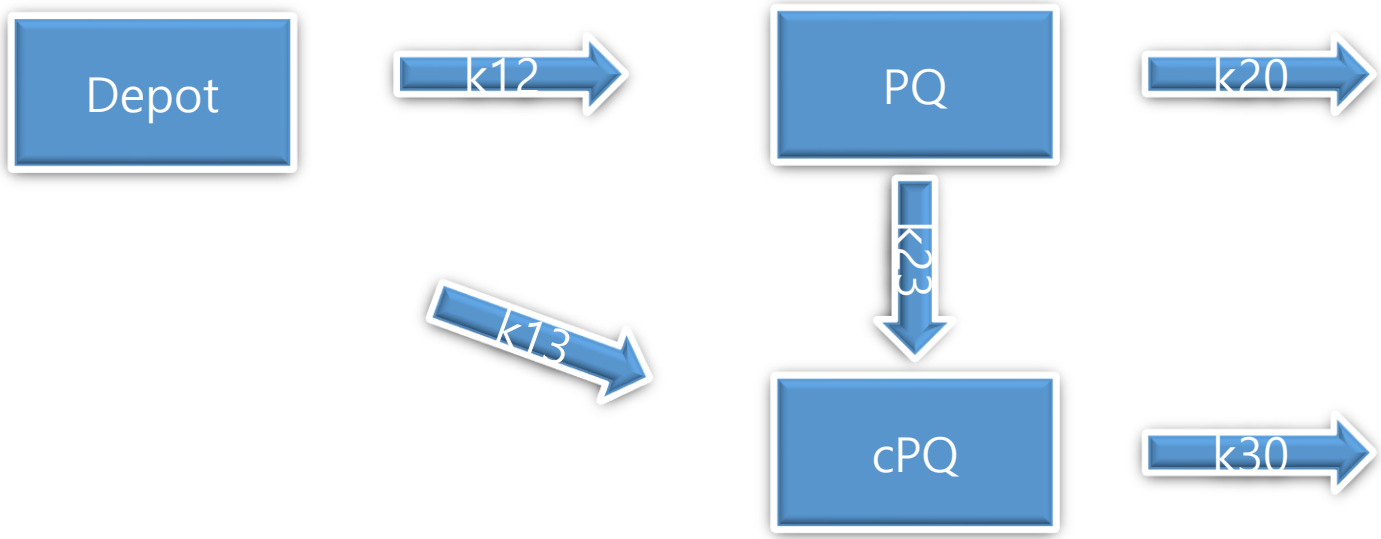
- Covariates were tested using stepwise covariate modeling (SCM) at significance levels of $P<0.05$ for forward addition and $P<0.01$ for backward deletion.

- Each parameter-covariate relationship was tested using linear and exponential function for continuous covariates, and linear function for categorical covariates.

- All analyses were performed using R ver 3.5.2 and NONMEM ver 7.3.

Result (model1)

- Structural model (schematic figure)



- K12 = (1-Fa)*KA, K13 = Fa*KA, K23 = FMET*(CL/V2), K20 = (1-FMET)*(CL/V2), K30 = CLM/V3

KA : aborption rate constant, **FMET** : fraction of conversion to cPQ, **Fa** : 1st pass effect, **CLM** : clearance of cPQ

Result (model2)

- Structural model (schematic figure)

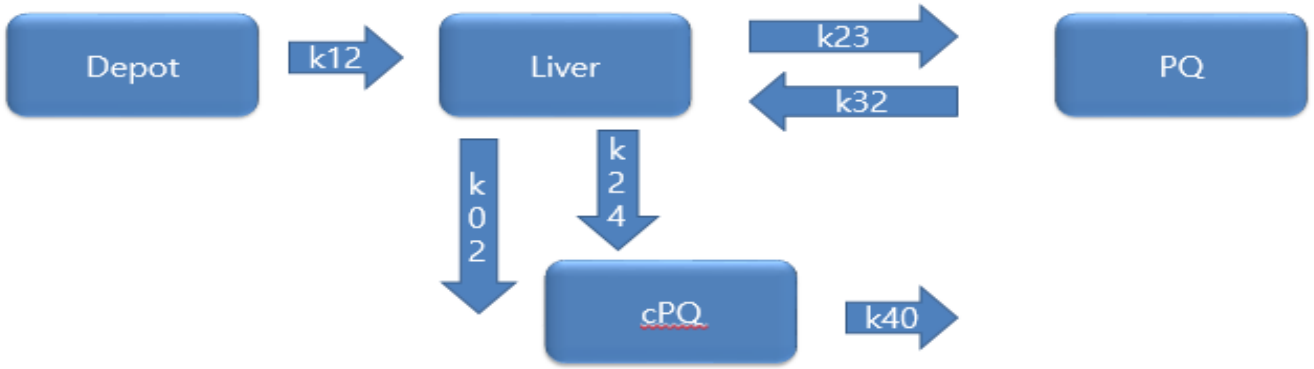


Figure 1. Schematic representation of the model.

- Parameter description

K12 = KA, K23 = QH*(1-EH)/V2, K32 = QH/V3, K24 = CLMAO/V2, K20 = CLCYP/V2, K40 = CLM/V4

KA : absorption rate constant

CLCYP : clearance of PQ by CYP2D6 pathway

CLMAO : clearance of PQ by MAO (monoamine oxidase) pathway

CLM : clearance of cPQ

EH : hepatic extraction ratio

QH : liver blood flow

Methods (model2)

- liver blood flow was fixed to 90L/hr and estimated liver volume of each subjects with equation from literature. Flow and volume parameters were allometrically scaled to body weight of 70kg. The exponents of the allometric models were fixed at 0.75 and 1 for flow and volume parameters, respectively.

- Estimated liver volume (LV)

[LV(mL) = 21.585 * $BW(kg)^{0.732}$* $BH(cm)^{0.225}$]

Result

- Model comparison

- Objective function value : Model 1 (3691) > Model2 (3675)
- Goodness of fit : not significantly different
- VPC result : not significantly different

We selected model 2 for it was lower in OFV and had more physiologic property by successfully estimating Vd of metabolite and 2 main clearance pathways.

Result

Parameter estimates

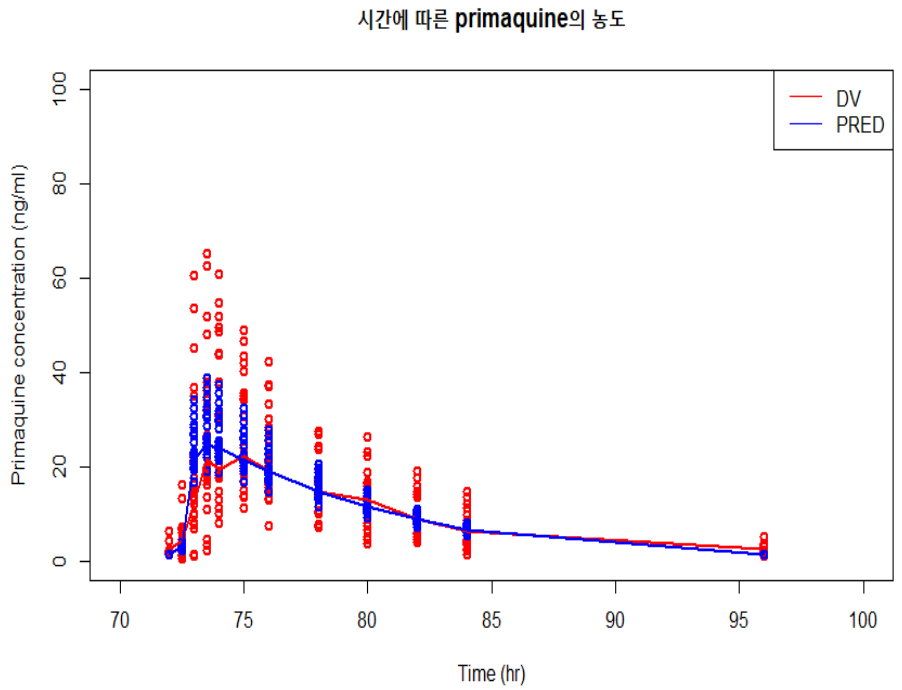
Theta	Description	Estimate	RSE (%)
	V3 (L)	268.8	7.3
	V4 (L)	21.6	17
	CLMAO (L/hr)	16.9	21.1
	CLCYP	26.6	14.9
	CLM	1	17.3
	KA	3.2	36.9
	ALAG1	0.47	1%
Omega	Description	Estimate (CV%)	RSE(%)
	V3	28.4	22.5
	CLMAO	37.8	16.7
	CLCYP	36.9	21.1
	KA	135.9	24.9
Sigma	Description	Estimate	RSE(%)
	Proportional (CV%)	34.48	10.1
	Proportional (CV%)	16.5	14.2
	Additive (SD)	26.3	29.8

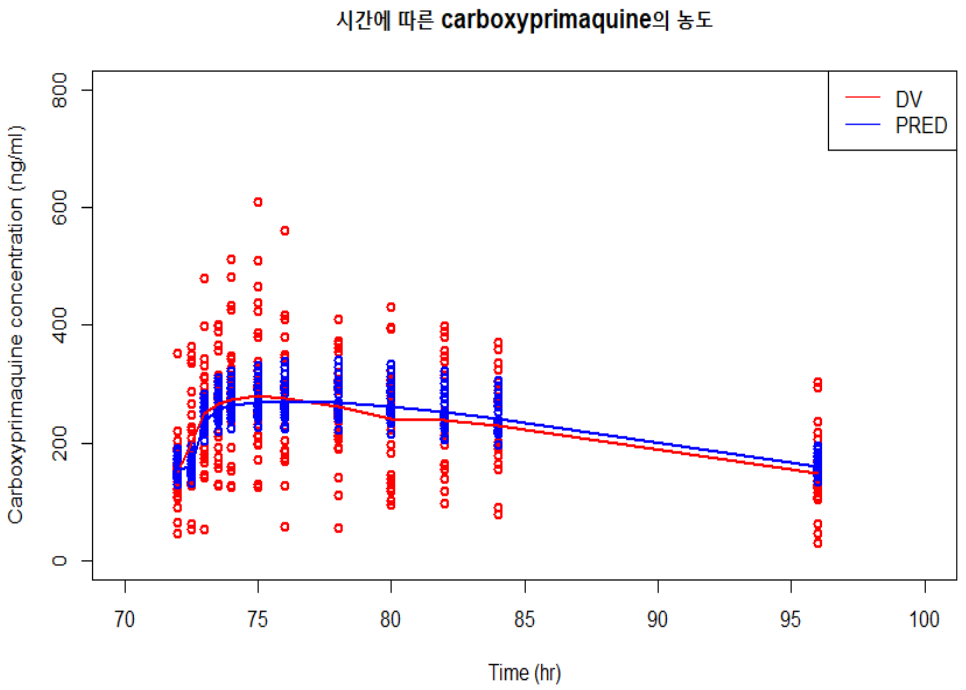
RSE: relative standard error **BSV: between-subject variability** **CV: coefficient of variation**

Result

Goodness of fit plots (GOF)

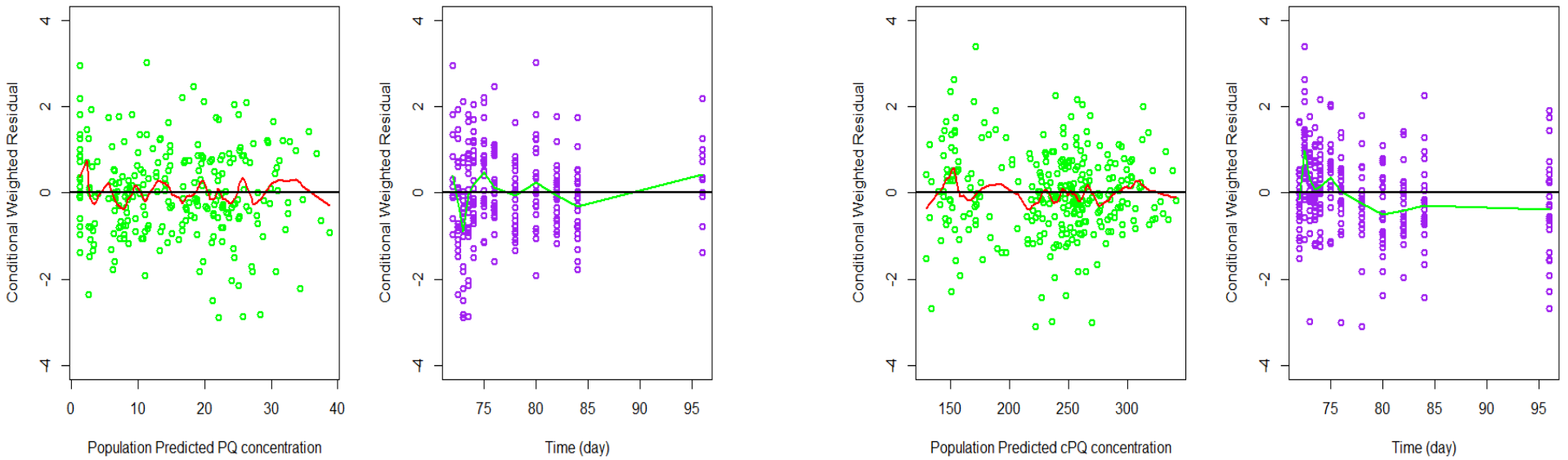
*Time versus population predictions (**PRED**) and observations (**DV**)*





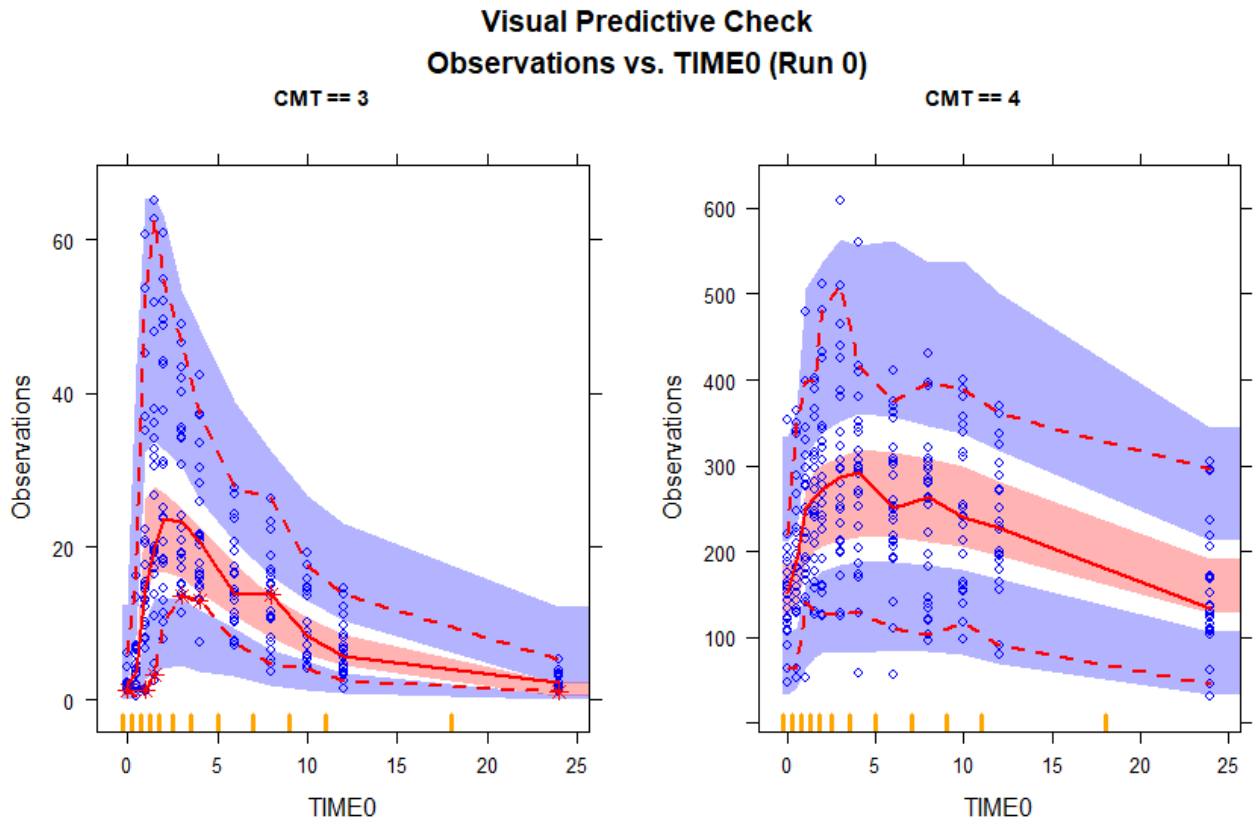
Result

*Population predictions and Time versus conditional weighted residual (**CWRES**)*



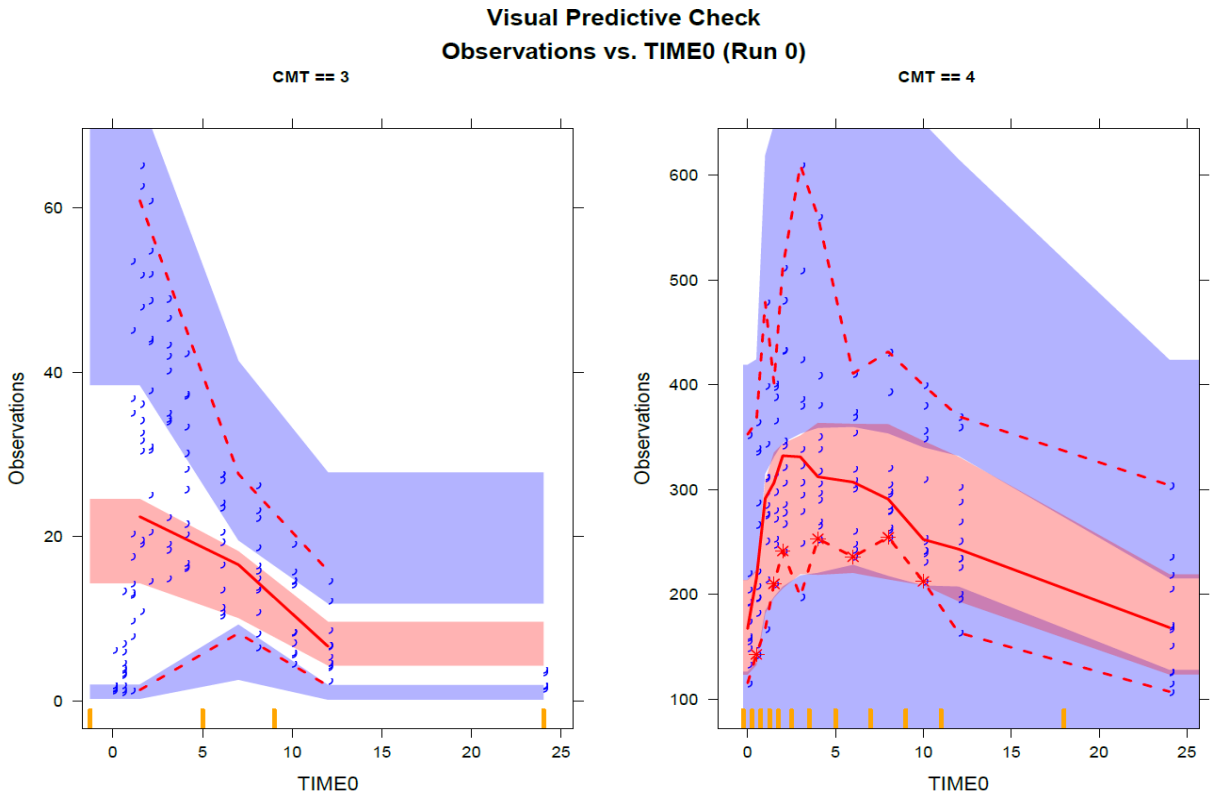
Result

*Visual Predictive Checks (**VPCs**)*



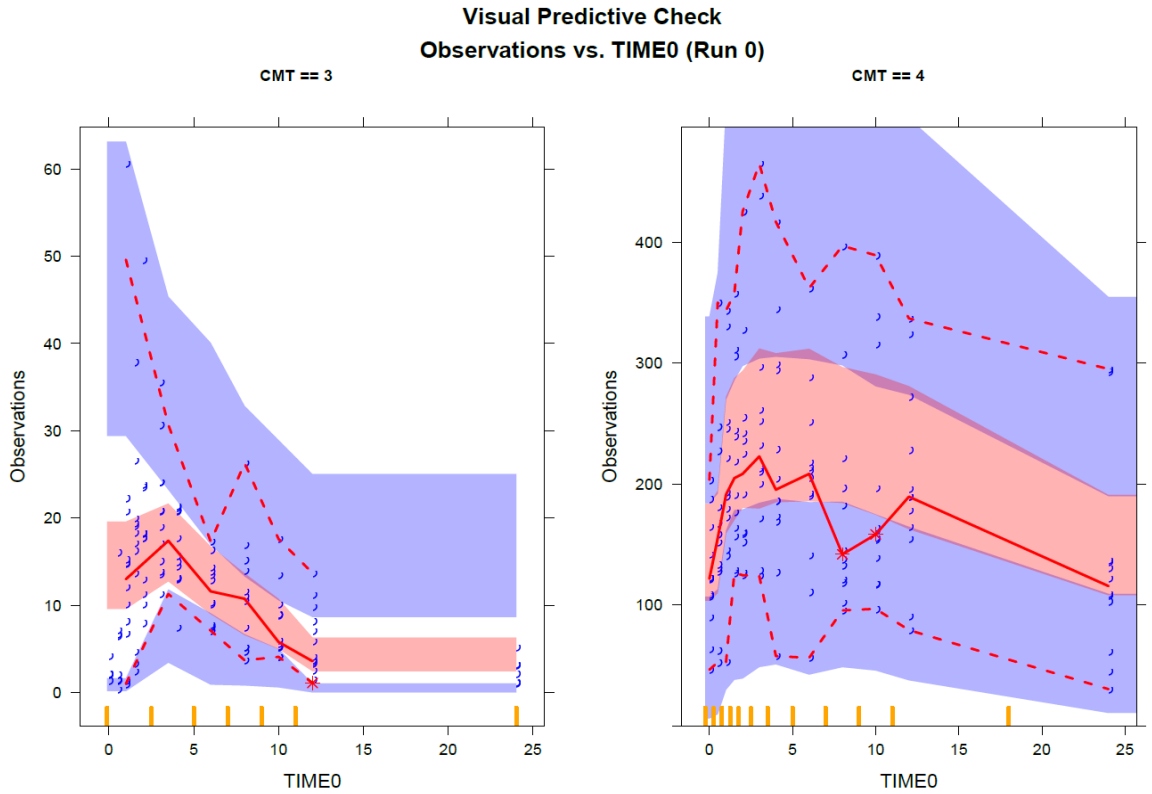
Result

*Visual Predictive Checks (**VPCs**) in normal weighted group*



Result

*Visual Predictive Checks (**VPCs**) in obese group*



Result

- Simulation results

: Using the model results, we simulated AUC and Cmax
with 1000 virtual individuals of obese group and light weighted group.

	min	Median	Mean	max
AUC normal	0.12	0.38	0.4	1.11
AUC obese	0.09	0.27	0.28	0.76
AUCM normal	1.34	6.75	6.87	15.57
AUCM obese	0.83	4.77	4.86	10.39

	min	Median	Mean	max
Cmax_normal	71.84	92.66	89.36	103.99
Cmax_obese	40.28	49.05	49.72	71.80

Result

- Simulation results

: Simulated AUC in obese group with adjusted dosing amount of primaquine, proportion to the AUC ratio.

	min	Median	Mean	max
AUC_normal (15mg)	0.12	0.38	0.4	1.1
AUC_obese (20mg)	0.12	0.36	0.38	1.02

Conclusion

1) Our population pharmacokinetic model successfully described the clinical data.

2) Body weight is the key covariate in terms of primaquine exposure that may affect the outcome of anti-malarial treatment. (dosing based on BWT is suggested instead of current “one size for all dose”)

3) Semi-mechanistic model was superior to the conventional compartmental pk model for :

- it successfully estimated separate clearance pathways of PQ
- Estimated the the volume of the metabolite, carboxy-primaquine, instead of fixing the value

Discussion (more findings)

1) Pharmacokinetic characteristics in patient group

- Metabolic clearance of monoamine oxidase (CLMAO) has reduced (by 64%) and the volume of distribution of primaquine has reduced (by 51%) in malaria infected group

: this result explains our NCA outcome that malaria infected patients showed higher primaquine concentration and lower cPQ/PQ ratio comparing to normal population

(But, this result was from only 2 patients : limitation)

Discussion (findings)

2) Covariate effect of CYP2D6 activity score on CLCYP

- Incorporating AS of CYP2D6 to the clearance parameter did not improve our model

END

Thank you for your attention !!