

A Mechanistic multi-compartmental Pharmacokinetic model for food effect of fenofibrate

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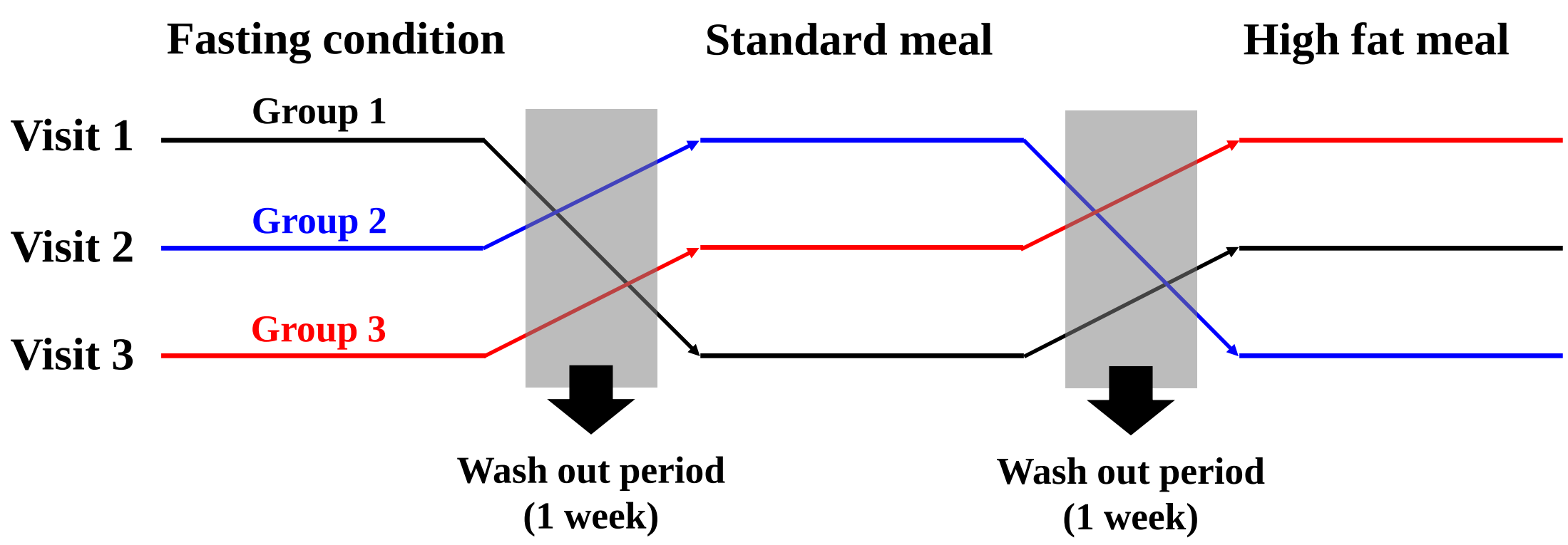
Objectives

Fenofibrate is a prodrug of the active metabolite fenofibric acid and it is used for hypercholesterolemia and hypertriglyceridemia. Absorption of fenofibrate is significantly different after consumption of food. The aim of this study was to develop a mechanistic population pharmacokinetic model of fenofibrate following food consumption in human.

Method

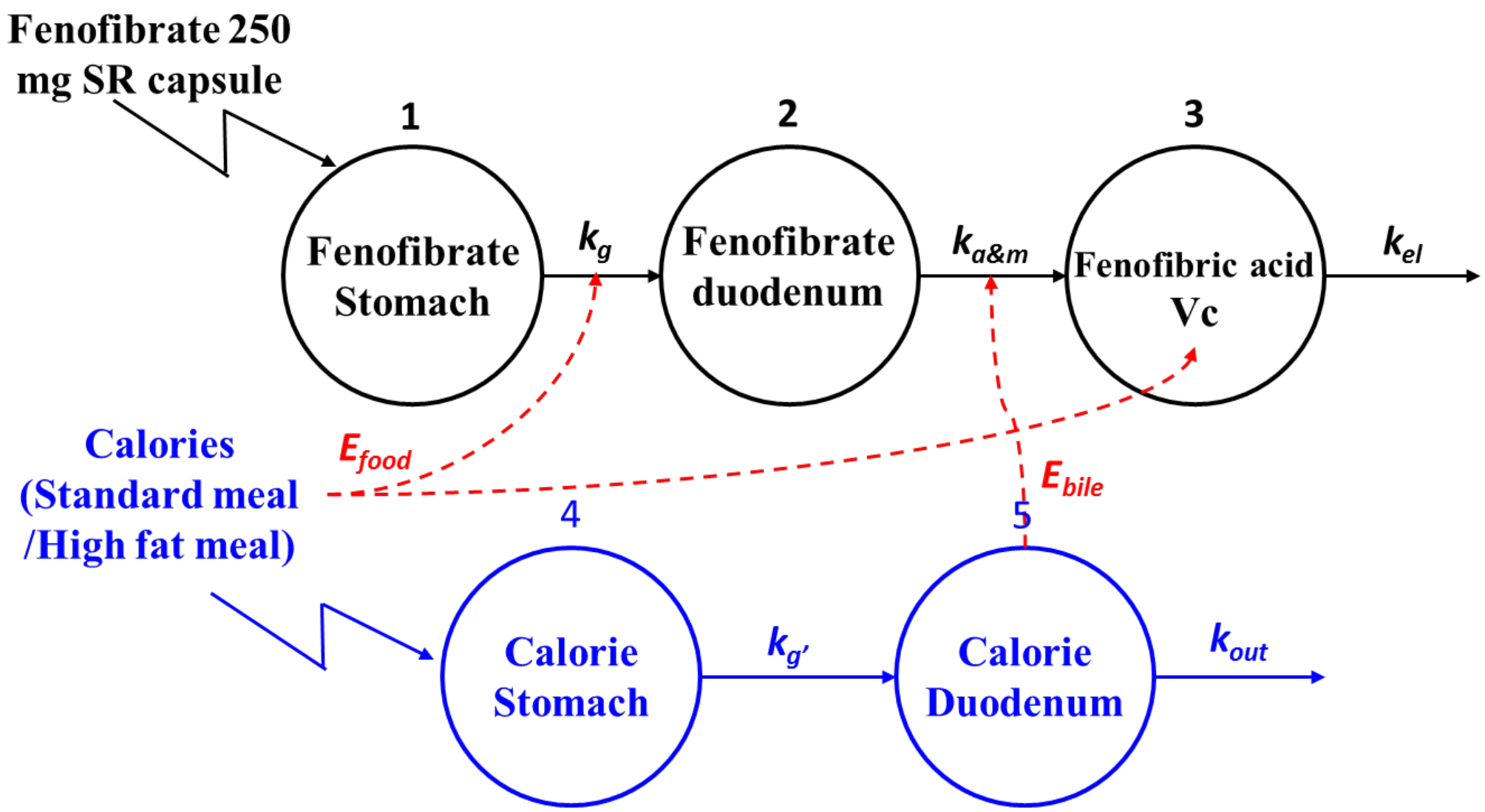
- Study design
 - A randomized, three-way crossover trial study was conducted in 24 healthy Korean subjects (13 male, 11 female).
 - Dose : Fenofibrate (250mg sustained release capsule)
 - Food type : Fasted condition, Standard meal, High fat meal
 - The subject received a single fenofibrate 250mg sustained-release capsule with 240mL of water 10minutes after consuming either a high-fat breakfast, a standard breakfast or no food (fasting condition).

	Standard meal	High fat meal
Calories	686.3 kcal	908 kcal
Fat content	19.9 %	35.5 %
Carbohydrate content	56.3 %	45.5 %
Protein content	23.9 %	19 %



- Sample collection and determination
 - Blood samples collection (6mL) : 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 hours after drug administration
 - Fenofibric acid which is a major and active metabolite of fenofibrate were determined by HPLC-UV

- Pharmacokinetic model
 - PK modeling was performed NONMEM ver 7.3 (ICON, USA)
 - Exponential model was used to explain the inter-individual variability and inter-occasion variability.
 - The constant coefficient of variation (CCV) model was used to explain the residual variability of the PK model



- k_g & k_g' : Absorption rate constant from stomach to duodenum
- $k_{a\&m}$: Absorption and metabolism rate constant of fenofibrate
- k_{el} : Elimination rate constant of fenofibric acid from central compartment
- k_{out} : Elimination rate constant of calorie from duodenum
- E_{food} : Food effect to absorption rate constant of fenofibrate from stomach to duodenum
- E_{bile} : Effect of bile to absorption and metabolism rate constant of fenofibrate

- MTIME option was used to explain the food effect after consuming breakfast.
 - $MTIME1 = \theta_i$
 - $MTIME2 = MTIME1 + \theta_i'$
 - $FLAG = MPAST1 - MPAST2$
 - $k_g = \theta_j * E_{food}^{FLAG} * e^\eta$
- Effect of calories amount in duodenum to absorption and metabolism rate constant of fenofibrate was tested using linear and nonlinear model.

- Model evaluation
 - Goodness of Fit plot, Visual Predictive Check (VPC) and bootstrap were implemented for internal validation
 - Bootstrap was done with 1,000 samples
 - VPC was performed by simulation of 2,000 samples using the final model
 - The 95% confidence interval of 5th, 50th, 95th percentile simulated concentration was obtained and graphically compared with the observed data

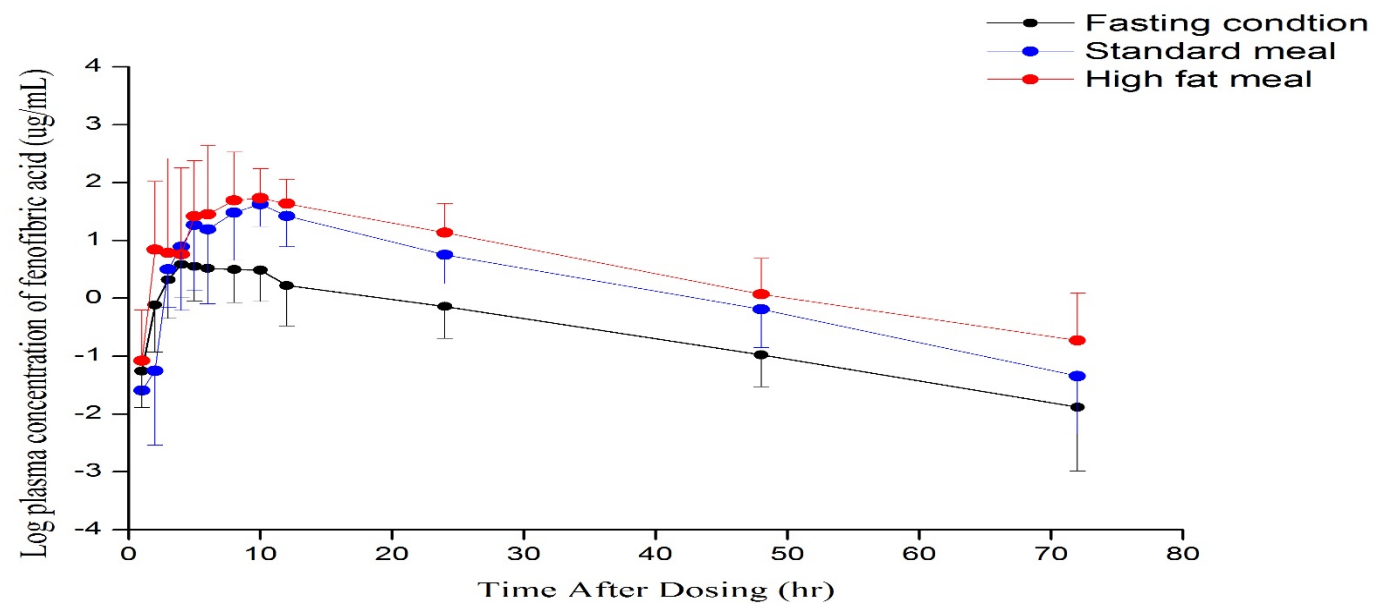
- Simulation scenarios
 - Oral administration of fenofibrate 250mg SR capsule q.d. for seven days.
 - Simulate 1000 samples each for four different food types
 - Following are the four different food groups for simulation:

	Group 1	Group 2	Group 3	Group 4
Calories	0 kcal	400 kcal	1280 kcal	1920 kcal
Food type	-	Low fat meal	High fat meal	High fat meal
Diet	-	Banana × 3 Boiled Egg × 2	Hamburger (236g), Fired potatoes (114g), Coke (425mL)	Fried Chicken (950g), Beer (500mL)

- After administration of fenofibrate 250mg SR for seven days, the plasma concentration profile of fenofibric acid were compared.
- After reaching steady state, $AUC_{168-192hr}$ of each group were estimated by Phoenix ver. 6.3. and compared difference between each group by ANOVA using SPSS ver. 21

Results

- Pharmacokinetic profile of fenofibric acid following food type after oral administration of fenofibrate 250mg SR capsule

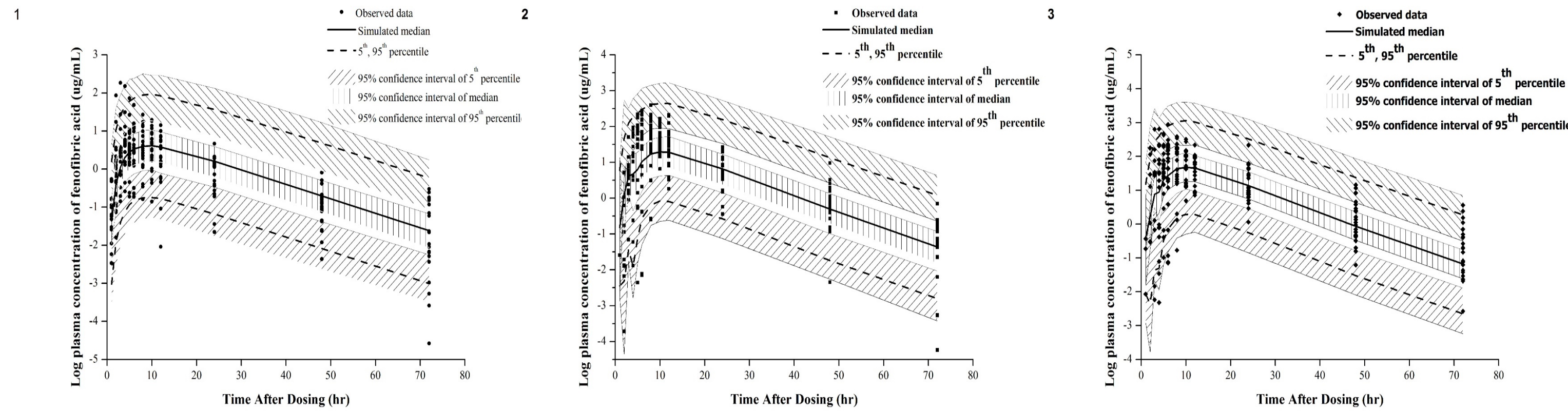


- Pharmacokinetic parameters and bootstrap results

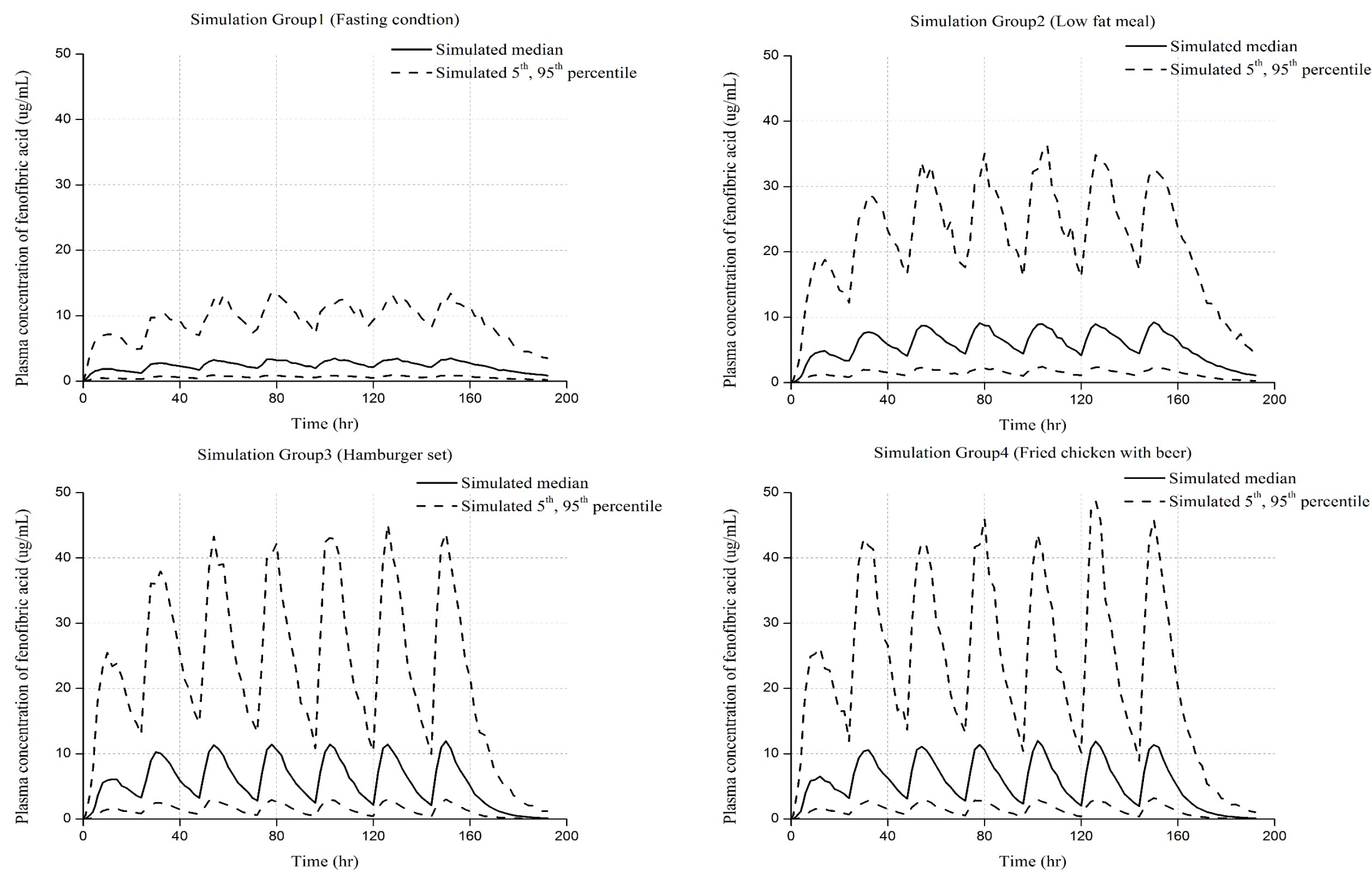
Parameters	Estimates (%RSE)	IIV (CV%) (%RSE)	IOV (CV%) (%RSE)	Bootstrap results of estimates 2.5%-97.5% percentile
$V_{stomach}$ (L)	1*	-	-	1*
k_g (hr ⁻¹)	0.836 (81.0%)	92.6% (33%)	-	0.16 ~ 1.51
$V_{duodenum}$ (L)	0.3*	-	-	0.3*
$k_{a\&m}$ (hr ⁻¹)	0.037 (9.0%)	-	-	0.034 ~ 0.040
V_c (L)	10 (42.3%)	16.9% (85%)	26.8% (71%)	5.77 ~ 14.23
k_{el} (hr ⁻¹)	0.37 (36.8%)	15.5% (65%)	47.6% (16%)	0.24 ~ 0.51
$V_{stomach}'$ (L)	1*	-	-	1*
k_g' (hr ⁻¹)	0.00978 (52.6%)	92.6% (33%)	-	0.0046 ~ 0.014
$V_{duodenum}'$ (L)	0.3*	-	-	0.3*
k_{out}' (hr ⁻¹)	0.324 (26.4%)	-	-	0.24 ~ 0.41
E_{bile}	0.0123 (45%)	-	-	0.0073 ~ 0.017
MTIME1	0*	-	-	0*
MTIME2	3.78 (30%)	-	-	2.68 ~ 4.90
E_{food1}	0.046 (43.5%)	-	-	0.026 ~ 0.066
E_{food2}	0.0973 (72.9%)	-	-	0.027 ~ 0.16
Residual Variability CV% (RSE%)				
Proportional error	63.8% (8.0%)			

* : Fixed parameter

- Visual predictive check results



- Simulation results



Group	Median $AUC_{168-192hr}$ (5%~95% percentile $AUC_{168-192hr}$)
Group 1 (Fasting condition)	460.33 (118.60 ~ 1769.80) $\mu\text{g}\cdot\text{hr}/\text{mL}$
Group 2 (Low fat meal)*	1096.16 (278.7 ~ 4245.98) $\mu\text{g}\cdot\text{hr}/\text{mL}$
Group 3 (Hamburger set)*	1097.05 (266.17 ~ 4408.69) $\mu\text{g}\cdot\text{hr}/\text{mL}$
Group 4 (Fried chicken with beer)*	1098.50 (268.87 ~ 4502.33) $\mu\text{g}\cdot\text{hr}/\text{mL}$

* : $p < 0.001$

Discussion

- In this study, we developed a mechanistic multicompartmental PK model to define the food effect on fenofibric acid after consumption of different types of food followed by oral administration of fenofibrate 250mg SR capsule.
- During development of PK model, some physiological compartments (Stomach, Duodenum) and parameters (k_g , k_g' , k_{out}) were added to explain simultaneous food effect on drug absorption.
- We assumed that amount of food(calories) in duodenum stimulate the secretion of bile acid, and bile acid affect the absorption of fenofibrate (E_{bile}) from GI tract to central compartment. Comparing linear and nonlinear bile effect on fenofibrate absorption, linear model was selected as it lowered objective function value.
- We also assumed that food intake will affect the gastric emptying rate constant (k_g) of fenofibrate. For explaining digestion time of food and fenofibrate after food intake, MTIME were estimated. During this digestion time, gastric emptying rate constant is affected by type of food in stomach (E_{food}).
- With our final model, all parameter values estimated by model were appropriate and the median values from the bootstrap results (n=1,000) accorded with those estimated by the model.
- In VPC with 2,000 samples, the 95% confidence interval of the 5th, 50th and 95th percentile of simulated data contained most of the observed PK data. Theses results showed that our model gave reliable parameters.
- Simulation were done for four food type scenarios and $AUC_{168-192hr}$ of fenofibric acid in steady state were compared. The $AUC_{168-192hr}$ of each group were significantly different.
- In conclusion, a mechanistic multicompartmental PK model of fenofibric acid after oral administration of fenofibrate 250mg SR capsule in healthy human was developed successfully. Simulation results showed that food consumption has high possibility of significantly increasing total exposure of fenofibric acid depending on the amount and type of food consumed. In further study, we will develop the mechanistic pharmacokinetic model considering food calories and food volumes.

Acknowledgment

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