Development of a semi-mechanistic absorption model for explaining effect of food on itraconazole

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Objectives

Oral administration of drugs has several advantages over other administration routes including lack of pain, easy to administer, portability and so on. However, it has certain limitation that can potentially be affected by many factors in gastrointestinal system. Consumption of food is one of the major factors that can affect GI system and consequently absorption of drug. The aim of this study was to develop a mechanistic absorption model for explaining effect of food on itraconazole by food type and volume.

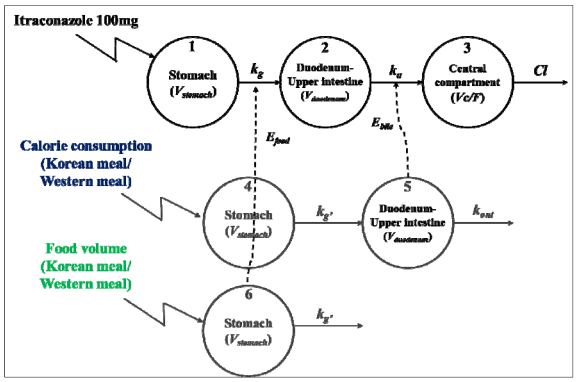
Method

- Study design
  - Pharmacokinetic data of itraconazole was pooled from 3 centers
  - The studies included in total 144 healthy Koreans and had three different food conditions (Fasting condition, Korean meal type, Western meal type)

	Center A		Center B		Center C	
Study design	Parallel, randomized study		Parallel, randomized study		Two-way crossover, randomized study	
Food condition	Fasting	Korean meal	Fasting	Western meal	Fasting	Korean meal
Dose	100mg tablet	100mg capsule	100mg tablet	100mg capsule	100mg capsule	100mg capsule
Dose regimen	Single oral dose under fasting condition with 200mL water	Single oral dose with 200mL water within 30 min after consuming a Korean meal	Single oral dose under fasting condition with 150mL water	Single oral dose with 150mL water 5min after consuming a Western meal	Single oral dose under fasting condition with 200mL water	Single oral dose with 200mL water within 30 min after consuming a Korean meal
No. of Subjects	20	20	40	40	24	
Sampling time	0, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48		0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72		0, 1, 2, 3, 4, 5, 7, 9, 12, 24, 48, 72	
Meal Composition	Steamed rice, boiled spinach seasoned with soy sauce, kimchi, bean-sprout soup, anchovy stir-fry		Bread meal (150g) with low fat milk (150mL)		Steamed rice, boiled spinach seasoned with soy sauce, kimchi, bean-sprout soup, anchovy stir-fry	

  - After collecting samples, plasma concentration was determined using HPLC-FD and HPLC-UV

- Semi-mechanistic pharmacokinetics model
  - Non-compartmental analysis was assessed by Phoenix ver.7.0 for identifying a difference of drug exposure between food type
  - PK modeling was performed using NONMEM ver7.3
  - 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': Gastric emptying rate constant from stomach to duodenum-Upper intestine
  - k_a: Absorption rate constant of itraconazole to central compartment
  - Cl : Clearance of itraconazole from central compartment
  - k_{out} : Elimination rate constant of calorie from duodenum-Upper intestine
  - E_{food} : Food volume effect to gastric emptying rate constant from stomach to duodenum
  - E_{bile} : Effect of bile to absorption rate constant of itraconazole

- For explaining changed gastric emptying rate constant after food consumption, MTIME option was used

  $MTIME1 = \theta_i$

  $MTIME2 = MTIME1 + \theta_i'$

  $FLAG = MPAST1 - MPAST2$

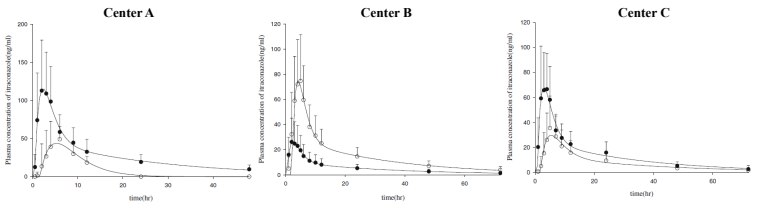
  $k_g = \theta_j * (1 + E_{food} * A(6))$

- Bioavailability of itraconazole was estimated in various condition like below
  - Fasted condition with 150mL water
  - Fasted condition with 200mL water
  - Korean meal with 200mL water
  - Wester meal with 150mL water

- Model evaluation
  - Goodness of fit (GOF) plot and Visual Predictive Check (VPC) and were implemented for evaluating final model
  - Prediction (PRED) and individual prediction (IPRED) versus observation, and conditional weighted residual versus time plot of final model was evaluated.
  - VPC was performed by simulation of 1,000 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

Results

- Pharmacokineitc profiles of itraconazole with three different food conditions in three centers

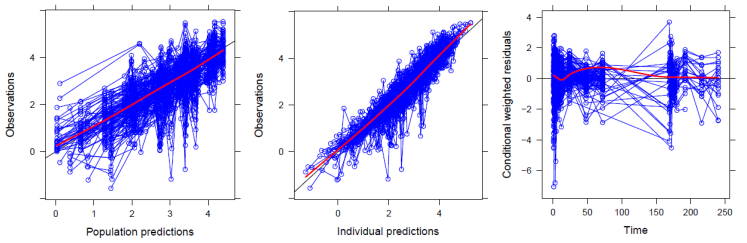


  - Center A & C: Under fasting condition (Closed circle) and after consuming a Korean meal (Open circle)
  - Center B: Under fasting condition (Closed circle) and after consuming a Western meal (Open circle)

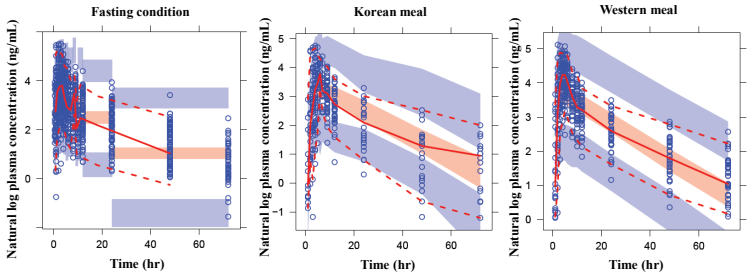
- Pharmacokinetic model
  - Two physiological & one systemic compartments for itraconazole and four physiological compartments for food condition was successfully developed

Parameters	Estimates (%RSE)	IIV (CV%) (%RSE)	Parameters	Estimates (%RSE)
k_g (hr^{-1})	1.43 (6.5 %)	-	*MTIME1 (hr)*	0.00001*
k_a (hr^{-1})	1.76 (7.4 %)	-	*MTIME2 (hr)*	12 (15.3 %)
V_c (L)	871 (3.3 %)	50.7 (7.8 %)	E_{food}	-1.63 (2.7 %)
CL (L/hr)	38 (3.6 %)	54.3 (7.1 %)	BA (Water 150mL)	0.151 (9.5 %)
k_{out} (hr^{-1})	1710 (25.1 %)	-	BA (Water 200mL)	0.393 (8.5 %)
E_{bile}	0.001 (5.8 %)	-	BA_Korean	-0.268 (14.7 %)
k_g' (hr^{-1})	0.279 (28.7 %)		BA_Western	0.243 (12.5 %)
Residual variability (% RSE)				
Proportional error	60.3 (3.4 %)			

- Model evaluation
  - GOF plot of final model



  - VPC plot of final model



Discussion

- In this study, we aimed to develop a semi-mechanistic absorption model for explaining effect of food on itraconazole by food type and volume.
- During the development of PK model, volume of some compartments were fixed with physiological value. ($V_{stomach}$: 0.047 L in fasting condition, 0.93L in fed condition, $V_{duodenum}$: 0.046 L)
- Our previous model for food effect (2015 PAGE, I-07) was used and updated for explaining effect of food volume on gastric emptying rate constant and food type on bioavailability of drug.
- Gastric emptying rate constant could be delayed after food consumption comparing with fasting condition and this delayed gastric emptying rate affected to absorption time of drug depending on volume of food. Our final model explained this phenomenon with Korean meal and Western meal (Korean meal has bigger volume than Western meal with same calorie)
- Generally, Western meal is more acidic than Korean meal and Korean meal acts like buffer. Because of this pH difference and buffering of gastric acid, exposure of itraconazole was lower in Korean meal comparing with fasting condition but in contrast, higher exposure in Western meal comparing with fasting condition. Our final model explained this difference between food type using different bioavailability.
- Observation versus PRED and IPRED showed linear relationship and conditional weighted residual versus time plot showed unbiased relationship. As a result of VPC, the 95% confidence interval of the 5th, median, 95th percentile of simulated data contained most of observed data. These results showed that our model gave reliable parameters and prediction.
- In conclusion, a semi-mechanistic absorption model for explaining effect of food on itraconazole was successfully developed. This final model has strength that can be quantified effect of food volume, type and calorie on drug absorption.

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