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 males, 11 females).
  - Each subject received fenofibrate 250mg sustained-release capsule in four food type scenarios.
  - Wash-out period was 1 week.

- Sample collection and determination
  - Blood samples collection (n=ml): 1, 2, 3, 4, 5, 6, 10, 12, 24, 48 hours after drug administration.
  - Fenofibrate which is a major and active metabolite of fenofibrate was determined by HPLC-UV.

- Pharmacokinetic model
  - PK modeling was performed NONMEM ver 7.3 (ICON, USA).
  - Goodness of fit was evaluated by the objective function value and the accuracy of parameter estimates.
  - Model validation was carried out using the leave-one-subject-out method.

- Model evaluation
  - Goodness of Fit plot, Visual Predictive Check (VPC) and bootstrap were implemented for internal validation.
  - Bootstrap was done with 1,000 samples.
  - We evaluated the estimated parameters using the base model.
  - We added an additional fixed parameter to explain simultaneous food effect on drug absorption.

- Simulation scenarios
  - Pharmacokinetic profile of fenofibric acid following food type after oral administration of fenofibrate 250mg SR capsule.
  - Simulation were done for four food type scenarios and AUC168-192hr of fenofibric acid in steady state were compared.

- Simulation results
  - Simulation results showed that food consumption has high possibility of significantly increasing total exposure of fenofibrate acid depending on the amount and type of food consumed.

Discussion

- In this study, we developed a mechanistic multi-compartmental PK model to define the food effect on fenofibrate after consumption of different types of food followed by oral administration of fenofibrate 250mg SR capsule.
- We also assumed that food intake will affect the gastric emptying rate constant (kEfood).
- We also assumed that food intake will affect the gastric emptying rate constant (kEfood) and the elimination rate constant of fenofibrate from central compartment (kout).
- We added an additional fixed parameter to explain simultaneous food effect on drug absorption.

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