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A Physiologically-based pharmacokinetic model adequately predicted the human pharmacokinetic profiles of YH4808, a novel potassium-competitive acid blocker, to treat gastric acid related diseases

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YH4808 is a highly potent, selective and reversible potassium-competitive acid blocker on H+/K+-ATPase under development for the treatment of gastric acid related diseases. The objectives of this study were to develop a human PBPK model optimized by human pharmacokinetic (PK) data, to predict the PK profiles of YH4808 using the PBPK model in various settings and to mechanistically understand the main factor of clinically observed nonlinear PK of YH4808 by exploring various drug-drug interactions (DDIs). A PBPK model was developed using SimCYP® based on the physicochemical properties, preclinical *in vitro* and clinical data of YH4808 (Figure 1), which was further refined using human plasma concentrations obtained from a single-dose ascending phase I clinical trial of YH4808. The absorption of YH4808 was described by the advanced dissolution, absorption and metabolism model. The Vmax and Km values for each CYP isozyme involved in the metabolism of YH4808 were determined from the *in vitro* Ki values using a graphical method (GraphPad Prism7, GraphPad Software, Inc., USA). The DDI potential for YH4808 with other co-administered drugs was predicted using the PBPK model by calculating the geometric mean ratio of the model-predicted and observed for the area under the concentration-time curve (AUC). The PBPK model adequately predicted the observed concentrations of YH4808 after a single and repeated oral administration at 100 mg (Figure 1 (b), Figure 2 (a)). However, the simulated plasma concentration profiles after repeated oral administration at 200 and 400 mg were not in line with the observed concentrations, particularly toward the terminal phase, showing some sort of non-linear accumulation (Figure 2 (b) & (c)). The PBPK model-based simulated AUC of YH4808 increased by 2.08-2.90 times when co-administered with phenacetin, mephenytoin and dextromethorphan, respectively, suggesting the metabolism of YH4808 may involve CYP1A2, 2C19 and 2D6, which was confirmed by *in vitro* DDI studies. These metabolic pathways can be saturated at a higher dose of YH4808 at >200 mg, resulting in a non-linear PK profile. A PBPK model adequately predicted observed concentrations of YH4808 in humans after a single and repeated oral administration. The saturation of liver metabolism by CYP1A2, 2C19 and 2D6 appears to be associated with the nonlinear PK characteristics of YH4808 after multiple oral administration. The PBPK model can be used to predict the PK profiles of YH4808 in various clinical settings.

Recent Publications:

1. Lee H A, Lee S, Yim S V, Kim B H (2017) Bioequivalence of two formulations of pregabalin 150 mg capsules under fasting conditions in healthy male subjects. International Journal of Clinical Pharmacology and Therapeutics. 55 (2): 171-176.
2. Lee H A, Leavens T L, Mason S E, Monteiro-Riviere N A, Riviere J E (2009) Comparison of quantum dot biodistribution with a blood-flow-limited physiologically based pharmacokinetic model. Nano Letters. 9 (2): 794-9.
3. Lee H A, Imran M, Monteiro-Riviere N A, Colvin V L, Yu W W, Riviere J E (2007) Biodistribution of quantum dot nanoparticles in perfused skin: evidence of coating dependency and periodicity in arterial extraction. Nano Letters. 7 (9): 2865-70.

Biography

Hyun A Lee is a PhD student at the Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University in South Korea. She is also a trainee in clinical pharmacology at the Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital. She has graduated from North Carolina State University (NCSU) in the USA with a Master's degree in Biomathematics (2010). Prior to that, she went to the University of Alabama (2001-2004), where she received a Bachelor's degree in Biology and Mathematics. After completing her undergraduate course, she worked as a Research Scientist at the Center for Chemical Toxicology Research and Pharmacokinetics (CCTRP) in NCSU. Her research area is physiologically based pharmacokinetic (PBPK) modeling and simulation to optimize new drug development. She has a lot of experience in PBPK modeling and simulation with new drugs.

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