

Modeling of blood pressure lowering effect for co-administration of valsartan and amlodipine

Young-A Heo^{1,2}, Yukyung Kim^{1,2}, Mijeong Son^{1,2}, Jinju Gug^{1,2}, DongWoo Chae^{1,2}, Hankil Son^{1,2}, Nick Holford³, Kyungsoo Park¹

¹ Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea

² Brain Korea 21 Plus Project for Medical Science, Yonsei University, Seoul, Korea

³ Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Background: The objective of this study was to develop population pharmacokinetic (PK) and pharmacodynamic (PD) model for antihypertensive effect of amlodipine and valsartan combined therapy.

Methods: Pharmacokinetic (PK) modeling was first carried out for both drugs using data collected from 48 healthy volunteers receiving a combined formulation of 10mg amlodipine and 160mg valsartan as a single dose. Systolic (SBP) and diastolic blood pressure (DBP) data were also collected from combination therapy. SBP and DBP data for monotherapies were gathered from literature search. Using constructed PK models, PD models for monotherapy of each drug and combination therapy were built with NONMEM 7.2 using the data collected from literature search and clinical trial respectively. Visual predictive check (VPC) was performed for model evaluation.

Results: Two-compartment model with zero order absorption best described the PK data of both drugs. For BP, monotherapy data for amlodipine was best fitted into a linear model and that for valsartan into linear (SBP) and E_{max} model (DBP). Combined therapy was best described with proportional interaction term, $(ADDR \times (1+ALPHA))$ where ADDR refers to the sum of BP lowering effects from amlodipine and valsartan monotherapies and ALPHA being the interaction term of combined therapy. Estimated ALPHA for SBP and DBP were -0.707 and -0.380 respectively, indicating the infra-additive interaction for both SBP and DBP, which was consistent with literature result about combination therapy of ARBs and CCBs.

Conclusion: The population PK model adequately described the observed concentrations and developed BP models successfully described the efficacy of combination treatment of amlodipine and valsartan in comparison to monotherapy of each drug.