Interpretation of Drug-Drug Interaction Study Results of Long Elimination Half-Life Drugs: Comparison of Conventional Bioequivalence Test Anda Model-Based Approach

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Objectives: For drugs with long elimination half-lives, multiple dosing drug-drug interaction (DDI) studies are challenging in the aspect of time, budget, and ethics from long-term administration of drugs to healthy subjects. Despite multiple dosing, steady state may not be accomplished, and conventional non-compartmental analysis (NCA) at this situation may give biased bioequivalence (BE) test results. Thus, we tried a a mixed-effects model-based BE test with simulated data to compare its performance with the conventional BE test.

Methods: We used data from a healthy subjects DDI study (amlodipine for 8 days and then amlodipine and drug X for the next 10 days). Full pharmacokinetic (PK) sampling for amlodipine was performed on day 8 and 18. and a amlodipine population PK model developed using the PK data of day 8 (NONMEM, Ver. 7.2) was used to simulate the amlodipine $C_{\text{max,ss}}$ and $\text{AUC}_{\tau,\text{ss}}$ for day 18. The conventional BE test results (day 8 versus day 18) were compared with the BE test results on simulated data (day 18 simulated versus day 18 observed).

Results: Plasma concentration-time profiles of amlodipine were best described by a two-compartment model with first-order kinetics. The geometric mean ratios (GMR) and their 90% confidence intervals (CI) of the conventional method were 1.187(1.135-1.239) for $C_{\text{max}}$ and 1.187(1.135-1.242) for $\text{AUC}_{\tau}$. The GMR for modeling based method were 0.997(0.978 -1.016) for $C_{\text{max}}$ and 0.973(0.962 -0.983) for $\text{AUC}$, that clarified the PK of amlodipine did not change by DDI.

Conclusions: The PK analysis method using modeling and simulation enabled us to distinguish between the effect of DDI and the effect of drug accumulation. Likewise, the proposed method may be useful to evaluate DDI of drugs with long elimination half-lives that may not reach steady-state within the study periods.

References: