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Development of PK/PD Model for the Antiplatelet and Cardiovascular Effects of Cilostazol using the Results of Bioequivalence Study

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In recent days, the bioequivalence(BE) study of domestic drugs on original drug are quite activated in Korea. This BE study provide not only the bioequivalence of test and reference drug but also produce the population pharmacokinetic(PK) parameters in normal healthy Korean. The BE study can also make it possible to establish a PK/PD model of the drug when the additional pharmacodynamic(PD) data are available.

The rationale for PK/PD modeling is to link PK and PD in order to establish and evaluate dose-concentration-response relationships and subsequently describe and predict the effect-time courses resulting from a drug dose. The relationships between plasma concentration of cilostazol and its inhibitory effect on platelet aggregation and cardiovascular effect in healthy humans were analyzed using a PK/PD model developed.

After single oral dose administration of 100 mg cilostazol to twenty healthy humans, time versus plasma concentration profiles were described over 48hr by HPLC determination. The effects of cilostazol on antiplatelet aggregation, blood pressure (BP) and heart rate (HR) were measured during the same period. The time courses of the plasma concentration of cilostazol and the antiplatelet aggregation (inhibition% and slope) or the cardiovascular effects (BP and HR) were analyzed with PK/PD modeling using ADAPT II program, respectively.

The plasma concentration-time course followed two-compartment model. Mean Cmax values after administration of the 100mg cilostazol was 735ng/ml at about 4hr. The maximum effect on antiplatelet aggregation was 30% and was appeared at 8hr. No significant difference in systolic blood pressure was noted during the study period. The maximal increase in HR was 15%, and the maximal decrease in DBP was 29%. Both the maximum change in diastolic blood pressure (DBP) and HR were detected at 6hr after administration of the drug. Developed PD

models were indirect response model with production of the response variable inhibited by the plasma concentration for the antiplatelet aggregation. Direct response model was tested for the change in DBP and HR. Plasma drug concentrations were linked to the observed effects via an effect compartment model with a sigmoid *E*max model. These PK/PD models could describe the relationship between cilostazol plasma concentrations and antiplatelet effect and cardiovascular effect successfully.