Pharmacokinetic/Pharmacodynamic Evaluation of Two Controlled Release Formulations of Nifedipine, GITS and Rhotard, in Healthy Volunteers

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Background : We evaluated the pharmacokinetic/pharmacodynamic characteristics of nifedipine GITS in normal volunteers and compared the pharmacokinetic characteristics of nifedipine GITS formulation (Adalat Oros®) and Rhotard formulation (Hadipine®).

Methods : The trial was a single-blind, randomized, 2-way crossover, reference formulation-controlled study in 12 healthy volunteers. There was a period of at least 7 days separating each treatment period to allow adequate washout. During the first study period, six subjects each received a single oral dose of Adalat Oros® after overnight fasting and blood samples were taken for up to 48 hours. Blood pressures and pulse rates were measured also. The other six subjects each received Hadipine® and were studied in the same way. After 1 week, the 12 subjects received the other drug and were studied in the same manner. Plasma nifedipine levels were assayed by HPLC methods.

Results - Pharmacokinetics : Hadipine®, compared to Adalat Oros®, showed an earlier Tmax (6.38±1.39 vs. 16.50±2.06, mean±SEM), higher Cmax (71.38±15.14 vs. 38.56±4.26) and a relatively greater fluctuation in plasma concentration profiles. After Hadipine® administration, 5 out of the 12 subjects had a plasma nifedipine concentration of less than 10 ng/mL at 24 hours after drug administration, but after Adalat Oros®, all of the 12 subjects had a concentration greater than 10 ng/mL at 24 hours after administration. T>10, the time that the plasma concentration exceeds 10 ng/mL, was significantly longer in Adalat Oros® compared to Hadipine (30.93±1.94 vs. 23.30±2.72, p=0.017). The 90% CI (confidence interval) for the ratio of means with reference to Adalat Oros® was 0.88~1.38 for AUC and 1.15~2.35 for Cmax, and neither was within the generally required range for bioequivalence (0.8~1.25). The 90% CI for the difference of means of Tmax with reference to Adalat Oros® was 34.1~88.5%, which was also not within the required range of 80~120%.

Pharmacodynamics : The diastolic blood pressure showed a statistically significant decrease at 4~14 hours after drug administration, but there were no significant differences between the 2 formulations in these normotensive subjects.

Conclusion : Hadipine was expected to show a greater fluctuation in plasma concentrations after multiple dosing compared to Adalat Oros®. Hadipine was shown not to be bioequivalent to Adalat Oros® because of the significant differences in Cmax, Tmax and the large variation in Cmax values. Therefore, future studies in hypertensive patients will be needed to examine the differences in therapeutic effects.