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Drug Interaction between Amlodipine and Simvastatin after Single Dose Administration in Healthy Subjects

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Background: Amlodipine is metabolized mainly by CYP3A and have a potential to interact with its substrates. Simvastatin, well-known CYP3A4 substrate, is frequently prescribed with antihypertensive drug. Coadministration of simvastain and amlodipine can lead to their pharmacokinetic interaction and be associated with an increased risk for their adverse reactions. This study is to evaluate the pharmacokinetic interaction between amlodipine and simvastatin when single oral dose of both drugs are coadminstered to healthy subjects.

Methods: In a randomized, open, 3-way crossover design, 20 healthy subjects were given single oral dose of amlodipine 10 mg, simvastatin 80mg, or both in each phase. Blood samples were collected upto 24 hrs in simvastatin only phase or 168hrs in amlodipine only / both dosing phase. Assay of simvastatin, simvastatin acid, and amlodipine in plasma were conducted using LC/MS/MS and their pharmacokineitc parameters were estimated using WinNonlin 5.0.

Results: Treatment with simvastatin had no significant effect on the AUC and the Cmax of amlodipine [215.02 (±67.30) ng*hr/mL and 4.08 (±1.11) ng/mL in the presence of simvastatin vs. 212.26 (±53.39) ng*hr/mL and 4.38 (±1.41) ng/mL in the absence of simvastatin]. Co-administration of amlodipine had no significant effect on the Cmax of simvastatin and simvastatin acid [11.72 (± 6.12) ng/mL and 3.98 (±2.34) ng/mL in the presence of amlodipine vs. 11.04 (±7.90) ng/mL and 3.41 (±1.26) ng/mL in the absence of amlodipine]. The AUC for simvastatin and simvastatin acid in the presence of amlodipine were significantly higher than that of simvastatin alone group [130.22 (± 89.89) ng*hr/mL vs. 88.43 (±59.73) ng*hr/mL and 67.57 (±42.75) ng*hr/mL vs. 48.02 (±22.83) ng*hr/mL] ($P < 0.05$ and < 0.001 respectively).

Conclusions: Simvasatin had no effect on the oral disposition of amlodipine, but amlodipine increased AUCinf of simvastain and its active metabolite, simvastatin acid, significantly (mean 1.6 and 1.4 fold respectively). These pharmacokinetic interactions of simvastatin and simvastatin acid when coadministered with amlodipine are likely result from inhibitory potential of amlodipine on CYP3A4. However, these interactions may not lead to alter the pharmacodynamic response when consider safety profile of simvastatin. It needs further evaluation of pharmacodynamic interaction between those drugs in sufficient number of subjects or patients.