

Effects of Cimetidine and Amiodarone on Pharmacokinetics of Theophylline in Healthy Korean Volunteers

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Background: Theophylline is the most potent drug among methylxanthine bronchodilator, and is used in asthmatic or chronic obstructive pulmonary disease patients. Cimetidine, amiodarone and theophylline may be prescribed together to treat patient with asthma, gastrointestinal discomfort and arrhythmia. Because theophylline has a narrow therapeutic index, small changes in plasma levels may result in therapeutic failure or adverse effects. These drugs are metabolized by cytochrome P450 (CYP) isozymes. Theophylline is metabolized by CYP1A2, however, the extent to which cimetidine and amiodarone interacts with this isozyme in vivo is not well known.

Methods: To evaluate drug interaction between cimetidine and theophylline in accordance with CYP1A2 genotype, 8 healthy non-smoking Korean volunteers were recruited. In an open-label, 2-period cross over study, 8 volunteers were administered a single oral dose of aminophylline 100 mg on day 1 of first period. After one week washout period, 8 volunteers were administered a same dose of aminophylline and 200 mg cimetidine. Blood were sampled until 36 hours after the administration of the drug. Plasma theophylline concentration was determined using high-performance liquid chromatography. 8 volunteers were genotyped using PCR-RFLP method to rule out polymorphic genotypic differences of CYP1A2, which could be a confounding factor. Same methods were applied to evaluate the drug interaction between amiodarone and theophylline in another 2-period cross over study.

Results: 16 subjects completed the study without any significant drug related adverse reaction. C_{max} of theophylline were elevated after coadministration of cimetidine (3.07 ± 0.93 and $5.72 \pm 1.51 \mu\text{g/ml}$, respectively) AUC_t, t_{1/2} and oral clearance of theophylline showed statistically significant differences ($p < 0.05$). Genotype of 8 subject showed no mutant genotype. Difference of pharmacokinetic parameters between theophylline alone and coadministration of amiodarone showed similar results.

Conclusion: Cimetidine and amiodarone dosing to theophylline increase C_{max}, AUC and decrease oral clearance in this population of healthy subjects. Therapeutic drug monitoring and dose adjustment of theophylline should be considered in patients receiving concurrent therapy with cimetidine or amiodarone.