Effect of intraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in subjects with known genotype of MDR1 3435C>T allele

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The effect of itraconazole on the disposition of fexofenadine, a known P-glycoprotein substrate, was evaluated in 12 subjects whose genotype of MDR1 3435C>T allele was predetermined. All subjects were given single oral dose of 180mg fexofenadine at 1 hour after single oral dose of 200mg itraconazole or placebo as placebo based double blind randomized crossover study. Blood samples were serially drawn and urine was collected upto 24 hours. Histamine induced wheal and flare sizes were also measured for 4 hours after fexofenadine dose to compare the pharmacodynamic effects.

In the phase of placebo pretreatment, the AUC and Cmax of subjects with MDR1 3435 T/T allele tend to be higher than those in subjects with C/C allele. The pretreatment of itraconazole significantly increased the AUC and Cmax (2.3 and 2.7 fold) and decreased Cl/F (2.6 fold) of fexofenadine compared to pretreatment of placebo in subjects with both genotypes as summarized in the following table.

		3435C/C	3453T/T
Cmax (ng/ml)	Placebo	505.0± 290.1	737.9 ± 333.9
	Itraconazole	1346.7± 306.3	1850.5± 530.6
AUC (ng · hr/ml)	Placebo	3999.7±1841.9	5403.0±2003.6
	Itraconazole	9210.0±2160.9	13906.9±2451.8
Cl/F (L/kg/h)	Placebo	778.0± 333.4	475.7± 135.1
	Itraconazole	292.9± 44.8	173.1± 32.0

The size of histamine induced skin flare tend to be decreased after itraconazole pretreatment compared to placebo treatment.

These results suggest that the disposition and antihistamine effect of fexofenadine were markedly influenced by co-administered itraconazole, a P-gp inhibitor, in addition to the moderate effect of MDR1 3435C>T genotype.