The Effects of CYP2D6*10 and Itraconazole on The Disposition and Adverse Effects of Haloperidol in Normal Subjects

박지영[1,2], 손지홍[1], 김경아[1], 정현주[1], 임동석[3], 신재국[1]

인제대학교 의과대학 약리학교실[1], 가천의과대학 약리학교실[2], 가톨릭의과대학 약리학교실[3]

This study was addressed to evaluate the effect of CYP2D6*10 and itraconazole (ITRA) as a CYP3A4 inhibitor on disposition and adverse effects of haloperidol (HAL).

For this, single 5mg HAL was orally given to 18 healthy subjects (8 subjects with CYP2D6*1/*1 (*1) and 10 subjects with CYP2D6*10/*10 (*10)) on 7th day of pretreatment with placebo or 200 mg/day of ITRA for 11 days, which was done as randomized double blind crossover manner. Plasma HAL concentrations, UKU side effect rate scales (UKU) and QTc prolongation for cardiac side effect were measured up to 96 hours after HAL dose.

The pharmacokinetic parameters of HAL are as follows:

	Pooled		CYP2D6*1/*1		CYP2D6*10/*10	
	Placebo	ITRA	Placebo	ITRA	Placebo	ITRA
Cmax (ng/mL)	1.4	1.6*	1.3	1.6	1.5	1.6
AUC (ng · h/mL)	21.9	32.6*	17.9	25.9*	26.0	39.4
$T_{1/2}$ (h)	12.6	27.1*	10.8	19.7	14.5	34.5*
CL/F (L/h/kg)	4.2	2.8*	4.7	3.6	3.6	2.0*

*$p<0.05$ compared to matched placebo

Dextromethorphan MR was significantly correlated with the CL/F, AUC, and half-life of HAL ($r>0.7$, $p<0.01$) after ITRA pretreatment. UKU score of *10 subjects tended to be higher than that of *1 subjects. However, the UKU score of *10 subjects pretreated with ITRA was significantly higher than that of the *1 subjects pretreated with placebo (1.9 ± 1.3 vs 0.4 ± 0.8, $p<0.05$). Neither the *10 genotype nor pretreatment of ITRA produced any significant change of QTc prolongation.

These results suggest that the disposition and in part the adverse effects of low dose HAL are influenced by CYP3A4 inhibition by ITRA and CYP2D6 activity.