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EFFECTS OF CYP2D6*10 GENOTYPE AND CYP3A4 INHIBITION ON THE DISPOSITION AND NEUROLOGICAL SIDE EFFECTS OF HALOPERIDOL IN HUMAN SUBJECTS

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Cytochrome P450 (CYP) 2D6 and CYP3A4 have been reported to be involved in the major metabolic pathways and formations of neurotoxic metabolites (HPP^+, $RHPP^+$) from haloperidol (HAL). However, no in vivo study has been addressed to the involvement of both CYP isoforms on the formation of toxic HAL metabolites.

After oral dosing of placebo or itraconazole (200 mg twice a day), a well known CYP3A4 inhibitor, into 9 healthy subjects with CYP2D6*1 and 11 subjects with CYP2D6*10 for 14 days, single 5 mg dose of HAL was orally administered on 7th day of each phase as a double-blinded, randomized, crossover manner. No significant difference in concentrations of HAL and reduced haloperidol were found, but its inactive and toxic metabolites (CPHP and HPP^+) recovered in 24 hours urine were significantly decreased after itraconazole pretreatment (80.31 μg vs 30.34 μg and 0.57 μg vs 0.23 μg, respectively). However, subjects with different CYP2D6 genotype showed no significant difference in the metabolite formation. UKU side effect rate scores were highest in CYP2D6*10 subjects pretreated with itraconazole among different groups of CYP2D6 genotype and placebo pretreatment.

In conclusion, CYP3A4 seems to mediate mainly on the metabolic pathways of HAL, while CYP2D6*10 genetic polymorphism is less likely to influence in human.