Plasma Concentrations of haloperidol are related to CYP2D6 genotype at low, but not high doses of haloperidol in Korean schizophrenic patients

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Aims : This study was carried out to evaluate the influence of the CYP2D6 genotype on the steady state plasma concentrations of haloperidol and reduced haloperidol in Korean schizophrenic patients.

120 Korean schizophrenic patients treated with various, clinically determined, doses of haloperidol (range 3-60, median 20mg/day) in monotherapy were recruited. CYP2D6 genotypes were determined by analysis of the CYP2D6*10 allele using allele-specific PCR and the CYP2D6*5 allele by long-PCR. Steady state plasma concentrations of haloperidol and reduced haloperidol were analyzed by HPLC.

Results : 23 (19.2%), 60 (50.0%), 1 (0.8%), 33 (27.5%) and 3 patients (2.5%) possessed the CYP2D6 genotypes *1/*1, *1/*10, *1/*5, *10/*10 and *10/*5, respectively. The allele frequencies of CYP2D6*1, *10 and *5 were 44.6%, 53.8% and 1.7%, respectively. Significant relationships between the given dose and the plasma concentrations of haloperidol (linear; R^2=0.60, p<0.0001) and reduced haloperidol (quadratic equation; R^2=0.67) were observed. Overall, the concentrations normalized for dose (C/D) of haloperidol were significantly different between the CYP2D6*1/*1, *1/*10 and *10/*10 genotype groups (One-way ANOVA; p=0.028). No significant differences between the genotype groups were found with respect to the C/D of reduced haloperidol (p=0.755). However, in patients with daily doses less than 20mg, significant differences in the C/D of haloperidol (p=0.003), but not of reduced haloperidol, were found between the three major genotype groups. In patients with doses higher than 20mg, no differences were found between the genotype groups for either haloperidol or reduced haloperidol. 68 patients (57%) used benztropine, an antimuscarinic agent. All 4 patients with a *5 allele (one together with *1 and three with *10) were found to use benztropine. The patients homozygous for the *1 allele seemed to need less benztropine than the patients with one or two mutated alleles (Fisher's exact test; p=0.036).

Conclusion : The dose-corrected steady state plasma concentrations of haloperidol, but not of reduced haloperidol, were significantly different between the CYP2D6*1/*1, *1/*10 and *10/*10 genotype groups when doses lower than 20mg of haloperidol were given. No differences were found at higher doses. These results suggest the involvement of CYP2D6 in the metabolism of haloperidol at low doses of haloperidol (<20mg daily), while another enzyme, probably CYP3A4, is the most important one at higher doses.