First-generation antihistamine-induced drowsiness and the CYP2D6 genotype

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Marked inter-individual variation in the activity of cytochrome P450 (CYP) 2D6 has been reported. The variation is, at least in part, due to the genetic polymorphisms. Therefore, genotyping of CYP2D6 might be useful in expecting individual responses to the substrate drugs. This study aims to investigate the relation between the CYP2D6 genotype and subjective drowsiness due to first-generation anti-histamines, CYP2D6 substrates.

The subjects were 276 Japanese college students, who have taken a first-generation anti-histamine or a combination cold medicine including one. Drowsiness due to the drug was rated subjectively as mild, moderate, or severe. The CYP2D6*1, *2, *4, *5, *10, *10D, *14A, *14B, *35 and *41 alleles were determined by LA-PCR and PCR-RFLP methods. The subjects were grouped into extensive, intermediate, or poor metabolizers by combination of the alleles. This study was approved by the ethics committee of Hokkaido Pharmaceutical University.

Only eight participants have taken a single agent of a first-generation anti-histamine whereas others (n=268) have taken a combination cold medicine. The number of the subjects who rated drowsiness as mild, moderate and severe was 156, 98 and 21, respectively (one missing) (Table). The allele frequency of CYP2D6*1, *2, *4, *5, *10, *10D, *14A, *14B, *35 and *41 was 0.384, 0.158, 0, 0.054, 0.382, 0, 0.005, 0.005 and 0.011, respectively. The number of extensive, intermediate and poor metabolizers was assumed to be 197, 65 and 13, respectively. The chi-square test could not show association between drowsiness and the CYP2D6 metabolic activity. However, in the 42 subjects who had taken PL Combination Granules(R) (Shionogi & Co, Ltd.) containing anti-histamine promethazine, intermediate and poor metabolizers tended to experience moderate to severe drowsiness more frequently than extensive metabolizers (P=0.050).

In conclusion, subjective drowsiness due to a combination cold medicine may not be an appropriate marker of the CYP2D6 metabolic activity. Further analysis is needed to investigate whether drowsiness due to PL Combination Granules(R) is related with CYP2D6 activity.