Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome.

Abstract:
Psychiatric pharmacotherapy with olanzapine is commonplace. We investigated the influence of CYP1A2*1F (-163A, rs762551) and serotonergic polymorphisms on olanzapine serum concentrations and clinical outcome in a naturalistic clinical setting. Included were 124 Caucasian psychiatric inpatients treated with olanzapine for at least 4 weeks with steady-state serum concentrations available for 73 patients. The CYP1A2*1F polymorphism was reported to affect the inducibility of CYP1A2. In our study population, CYP1A2*1F/*1F genotype alone resulted in a 22% reduction of dose-/body weight-normalized olanzapine serum concentrations compared to homo- and heterozygote carriers of CYP1A2*1A (both groups without inducers). This effect was independent of the well-known effect of inducing agents (here tobacco smoke and carbamazepine which led to on average 28% lower concentrations in CYP1A2*1A carriers and 26% lower concentrations in CYP1A2*1F/*1F carriers). Consistently, patients with the CYP1A2*1F/*1F genotype taking inducers had 22% lower concentrations compared to CYP1A2*1A carriers taking inducers. The influence of genotype alone remained significant after Bonferroni's post hoc test. Higher olanzapine concentrations were significantly correlated with better improvement of paranoid and depressive symptoms in
patients with schizophrenic disorders (Spearman's r=0.5, P=0.026 and P=0.006, respectively). No relationship between serum concentrations and the side effects (DOTES) score was detected. However, patients with the 5-HTR2A intron 2 (rs7997012) AA genotype suffered from more pronounced side effects compared to carriers of the GA or GG genotype (P=0.018 and P=0.002). Short-term weight gain under olanzapine therapy was significantly lower for 5-HTR2C -759 T-allele carriers (P=0.011). Our data suggest that the CYP1A2*1F/*1F genotype exhibits a significant influence on olanzapine concentrations independent of other inducing factors. Thus, CYP1A2*1F genotyping may be useful for clinical treatment decisions given the fact that olanzapine serum concentrations correlated with treatment response. Side effects and weight gain, however, seem to be more influenced by serotonergic polymorphisms.

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