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CYP1A2*1D and *1F Polymorphisms Have a Significant Impact on Olanzapine Serum Concentrations.

Abstract:
Although several polymorphisms in olanzapine-metabolizing enzymes have been identified, the clear role and benefit for pharmacotherapy remain uncertain. The aim of the study was to investigate the potential influence of polymorphisms in the CYP1A2 gene (*1D,*1F), in the UGT1A4 gene (*3), and in the POR gene (rs2302429) on olanzapine serum concentrations and the clinical outcome. Ninety-eight white inpatients who received olanzapine as part of their treatment for at least 4 weeks were included in the retrospective investigation. Moreover, a sample of 209 inpatients receiving olanzapine or clozapine was built to investigate the influence of the relevant polymorphisms CYP1A2*1F, *1D, and CYP1A2 inducers on the clinical outcome. Carriers of the delT-allele (*1D) developed significantly higher dose-corrected olanzapine serum concentrations (analysis of covariance; P< 0.001, delT + delTdelT: 3.1, TT: 1.6 ng·mL·mg; adjusted model including the confounding factors age, sex, baseline weight, CYP1A2*1F genotype, and concomitant CYP1A2 inducers). Moreover, the CYP1A2*1F (AA) genotype also revealed a significant impact on olanzapine serum concentrations according to the analysis of covariance model (P = 0.028; CC + CA: 2.05, AA: 1.44 ng·mL·mg). The other polymorphisms studied revealed no significant influence. Regarding response and adverse effects, a higher increase of
weight could be observed in schizophrenic Paranoid Depressive Scale (responder: +5.7 vs nonresponder: +1.8 kg; P = 0.007) and Clinical Global Impression responders (4.6 vs 1.8 kg; P = 0.017). No direct correlation between olanzapine serum concentrations and response or weight gain could be detected. Patients with at least 2 factors promoting higher serum concentrations (no CYP1A2 inducer, *1D delT-allele, or *1F C-allele) showed a better response according to the Paranoid Depressive Scale (P = 0.002) and a significant correlation with the Clinical Global Impression Scale-2 after 4 weeks (n = 193, r = -0.177; P = 0.005). We, for the first time, identified a significant influence of polymorphisms in CYP1A2 in combination with CYP1A2 inducer status on the clinical outcome. Therefore, genotyping for CYP1A2*1D and *1F may be a useful tool for dose optimization and identification of high-risk patients. Further and larger studies are needed before genotype-based dosage recommendations can help patients treated with CYP1A2 metabolized drugs.