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The authors report no competing interests.

Safety of Aripiprazole: High Serum Levels in a CYP2D6 Mutated Patient

TO THE EDITOR: We present a patient with high serum levels of aripiprazole caused by a common genetic modification in CYP2D6.

A 51-year-old female patient diagnosed with schizophrenia was admitted to our clinic. Little antipsychotic effect being observed, the dose of aripiprazole was increased from 15 mg to 30 mg per day. Within approximately 2 weeks, progressive symptoms of lethargy and memory loss were evident.

After testing blood samples, the serum level of aripiprazole in our patient turned out to be 2990 ng/ml, approximately seven times the expected plasma concentration at the maximum dose of 30 mg per day (1).

Since aripiprazole is metabolized by CYP2D6 and CYP3A4 (2), testing for a genetic polymorphism in these genes was initiated, showing a substitution of G1934→A on both alleles of the CYP2D6 gene (homozygote CYP2D6*4/*4), corresponding with the suspected slow metabolism. Pharmacokinetic interactions with CYP3A4 were excluded, since our patient did not use concomitant medication, herbals or grapefruit juice. When aripiprazole was substituted by quetiapine 400 mg daily, the adverse symptoms improved.

The high serum levels of aripiprazole, not the adverse events, are disconcerting. Poor metabolization is seen frequently, with prevalence rates in Caucasians of 7% and of 1%–4% in Asians and black Americans (3, 4). Additionally, although aripiprazole is relatively safe in cases of acute intoxication (5), preclinical safety data revealed significant toxic effects in female rats, including 1) dose-dependent adrenocortical toxicity and 2) increased incidence of adrenocortical and combined carcinomas at three to 14 times, respectively, and 14 times the mean AUC at 30 mg a day (2). Our patient showed serum levels in the range of the toxic effects in animal studies. The concordance rate of toxicity in humans with animal studies is 71% (6). Assuming our patient to represent all poor metabolizers, many patients would potentially be at risk of long-term toxicity because of the good tolerability of aripiprazole (1).

Since poor metabolizing occurs regularly, we recommend drug monitoring (expected plasmaconcentration at 15 mg and 30 mg daily: 206-278 ng/ml and 320–584 ng/ml, respectively [2]) after 14 days of treatment, when a steady state is expected as well as further safety studies in poor metabolizers.

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Corrections

In the Clinical Case Conference "An Interaction Between Aspirin and Valproate: The Relevance of Plasma Protein Displacement Drug-Drug Interactions" (Am J Psychiatry 2006; 163:1891–1896), the units for valproate blood levels were given as "ng/ml." They should be "μg/ml."

In the article "Differences in Brain Chemistry in Children and Adolescents With Attention Deficit Hyperactivity Disorder With and Without Comorbid Bipolar Disorder: A Proton Magnetic Resonance Spectroscopy Study" (Am J Psychiatry 2006; 163:316–318),the NIMH grant number in the acknowlegments should have been MH-01978.