In Case of Treatment-Resistant Schizophrenia, Pharmacogenetic Tests Could Be Helpful to Explain the Resistance and the Selection of New Drugs

Tedaviye Dirençli Şizofreni Vakasında, Farmakogenetik Testler Direncin Açıklanmasında ve Yeni İlaçların Seçiminde Faydalı Olabilir

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ABSTRACT Genetic variations among people in the genes encoding cytochrome P- 450 dependent monooxygenase metabolism may lead to differences in the efficacy and toxicity of antipsychotic drugs metabolized by this enzyme system. In this article, we present a 20-year-old, Caucasian man with schizophrenia who was resistant to antipsychotic medications and electroconvulsive therapy. His symptoms did not decreased after he was medicated by clozapine (300mg/day), risperidon (6 mg/day), quetiapine, piracetam, haloperidol (40mg/day), zuclopenthixol (50 mg/day), biperiden and vitamin B. At the time of admission, liver and renal function tests were normal, and results of routine laboratory tests were within normal limits. Analysis of the patient's cytochrome P-450- dependent monooxygenase genotype and phenotype indicated that his unusual response to antipsychotic medications might be explained by ultrarapid CYP1A2 metabolism and intermediate CYP2D6 metabolism. In this case report we suggest the clinical usefulness of pharmacogenetic testing in individualized dosage adjustments of antipsychotic medications.

Key Words: Clozapine; pharmacogenetics; risperidone; cytochrome P-450 CYP2D6;
cytochrome P-450 CYP1A2; schizophrenia; smoking

ÖZET Sitokrom P450' ye bağımlı monooksijenaz enzim sisteminde görülen genetik polimorfizmler, bireyler arasında ilaç cevabında görülen farklılıkların en önemli sebeplerinden bir tanesidir. Bu makalede, antipsikotik ilaçlara ve elektrokonvulzif tedaviye dirençli olan 20 yaşında kafkas kökenli erkek şizofreni hasta olgusu sunulmaktadır. Rutin laboratuvar, karaciğer ve böbrek fonsiyon testleri normal olan vaka 4 yıldır çeşitli merkezlerde yapılan tedavilere ve hastanemizde uygulanan klozapin (300mg/gün), risperidon(6 mg/gün), ketiyapin (300 mg/gün), pirasetam (2,4 g/gün), haloperidol (40mg/gün), zuklopentikzol (50 mg/gün), biperiden (2 mg/gün) ve vitamin B tedavisine cevap vermemiştir. Tedaviye direnç nedeni ile yapılan farmakogenetik testler hastanın antipsikotik ilaçlara cevap vermeyişinin ultrarapid CYP1A2 enzimi ve intermediate CYP2D6 enzimi metabolizması metabolizması ile açıklanabileceğini göstermiştir. Bu olgu raporunda antipsikotik ilaçların dozlarının bireyselleştirilmesinde farmakogenetik testlerin klinik faydasını vurgulamaktayız.

Anahtar Kelimeler: Klozapin; farmakogenetik; risperidon; sitokrom P-450 CYP2D6;
sitokrom P-450 CYP1A2; şizofreni; sigara içme

The nature of drug response is highly complex, involving genetic and nongenetic factors, like environmental factors including age, gender, hepatic and renal status and, additionally, nutrition, smoking or alcohol consumption. There is an important unexplained individual differences in treatment with antipsychotics, a proportion of patients given a regular dose do not respond properly or they experience with limiting side

effects.[1] Many association studies have been carried out, with genes coding for either the pharmacokinetic (encompassing the processes that influence bioavailability) or pharmacodynamic (targets of drug action) pathways. To date, many pharmacodynamic studies concerned the candidate genes that were associated either by the aetiopathology of schizophrenia or by the putative pharmacological mechanisms of the drugs.[1] Cytochrome P450 (CYP) hepatic enzyme variants affect the drug metabolisms in most psychiatric medications.[2,3] Various enzymes of the cytochrome P450 family play a vital role in the elimination of antipsychotics and therefore influence their efficacy and toxicity. An increasing number of examples describing differences in antipsychotic response as a result of genetic polymorphisms have been reported.[4] CYP enzymes show individual differences in activities due to genetic variants constituting multiallelic systems that express a variety of phenotypes. These can be distinguished as poor, intermediate, extensive or ultrafast metabolizers. Mutant alleles differ from normal-functioning alleles by point mutations, gene deletions or gene duplications.

In particular, CYP2D6, an abundant hepatic enzyme involved in the biotransformation and elimination of many antidepressant and antipsychotic medications, has been thoroughly investigated and associated with propensity to develop toxic reactions.[5-8] Similar functional polymorphisms have been observed in the genes coding for CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes. CYP2C19 may be clinically relevant for the metabolism of antidepressants, but CYP1A2 and CYP3A4 are the main metabolic pathways of most commonly used antipsychotics, including olanzapine, risperidone, aripiprazol, and clozapine.[9]

In this report, our aim is to describe a patient who presented schizophrenic symptoms despite having received all antipsychotic medications, and his pharmacogenetic test results.

CASE REPORT

A 20-year-old Caucasian man with a history of schizoprenia was hospitalized. His body weight was 70 kg and he was 185 cm in height. His family history have no characteristic for schizoprenia and any other psychiatric disease. Further history obtained from the patient indicated that he had been diagnosed with schizoprenia at the age of 16. He was hospitalized in Switzerland for a period of two years and he was resistant to all antipsychotic medications and electroconvulsive therapy (ECT). Due to initial examining, he presented irritable, labile and agitated mood, lack of sleep and racing thoughts. Medical and neurological studies including a computerized tomography of the brain were unremarkable. He was smoking one pack a day. His medications included clozapine (300mg/day), risperidon (6 mg/day), quetiapine (600 mg/day), piracetam (800 mg/day), haloperidol (40mg/day), zuclopenthixol (50 mg/day), biperiden (2 mg/day) and vitamin B. He did not show any progression to the medication, and semptoms did not decreased. Although antipsychotic medications commonly produce extrapyramidal symptoms as side effects, these symptoms (acute dyskinesias and dystonic reactions, tardive dyskinesia) was not observed in these patients. At the time of admission, his liver and renal function tests were normal and the results of routine laboratory tests were within the limits. This patient underwent CYP450 genotyping after informed consent was obtained.

It was decided that implementation of pharmacogenetic testing in treatment-resistant patients. Risperidone is metabolized by CYP2D6 and CYP3A4. Quetiapine is metabolized by CYP2D6, CYP3A4. Piracetam is excreted unchanged in the urine. Halloperidol is metabolized by CYP2D6, CYP3A4. Zuclopenthixol is metabolized by CYP2D6. Biperiden is metabolized by hydroxylation. We thought that were suitable pharmacogenetic tests for CYP1A2, CYP2D6, CYP3A4 enzymes. But our laboratory could have detected CYP2C9, CYP2C19, CYP2D6, CYP1A2 enzyme. The causes of resistance to the drug treatment of patients, we had detected CYP2D6, CYP1A2 enzymes and with the aim to select new drugs to patients, we had detected CYP2C9, CYP2C19 enzymes.

CYP450 genetic testing revealed that the patient had *1/*5 genotype for *CYP2D6*, with predicted phenotype of intermediate metabolizer, and

for *CYP1A2* genotype, he had *1A/*1F alleles, again with predicted phenotype of ultrarapid metabolizer. He had *CYP2C9* (*1/*2) and *CYP2C19* (*1/*2) genotypes, all were with the predicted phenotype of extensive metabolizer.

DISCUSSION

There is a growing body of literature supporting the contribution of genetic variability to the mechanisms responsible for antipsychotic medications.

In the present report, schizophrenic patient, who is a smoker, with the *CYP1A2* *1A/*1F genotype, observed a lower response to the clozapine treatment rate. Clozapine is an atypical antipsychotic drug applied for the treatment of resistant schizophrenia. A clinical problem in the use of clozapine is the very wide interindividual range of drug doses. Individualized drug therapy is necessary for treatment with clozapine.[11] CYP1A2 is the main cytochrome P450 (CYP) isoenzyme involving in the hepatic metabolism of clozapine. Our patient genetic testing revealed that he had *CYP1A2* *1A/*1F, and this was with the predicted phenotype of ultrarapid metabolizer. It means that clozapine, substrate of CYP1A2, is more likely to be removed from the body. It is known that some variables such as gender, age, smoking habits, coffee drinking and the use of CYP1A2 interacting co-medication can influence clozapine pharmacokinetics.[12] Men seem to have a higher activity relative to women for CYP1A2.[13] The recommended therapeutic plasma levels of clozapine are between 350 ng/ml and 420 ng/ml and most patients need to be treated with at least 300-600 mg/day of clozapine to reach these levels.[13] Smoking is a potent inducer of CYP1A2 enzyme activity, resulting in significant lower clozapine serum concentrations in smokers compared with non-smokers.[14] At similar doses, 20-40% lower mean serum concentrations of clozapine were found in smokers compared with nonsmokers.[14] It has been suggested that an average female nonsmoker requires low clozapine dosages(around 300 mg per day) to reach therapeutic levels whereas an average male heavy smoker requires high dosages (around 600 mg per day).[15] Therefore if the patient decides to stop

smoking doses of clozapine should be decreased immediately on the cessation of heavy smoking. Consequently, *CYP1A2**1F polymorphism, male gender and smoking are significant determinants of the success of clozapine treatment. Determination of *CYP1A2**1F polymorphism may be helpful in predicting treatment response especially in smoking psychotic patients.

It has been also shown that the plasma concentration of clozapine increased markedly in patients who also received fluvoxamine, a CYP1A2 inhibitor.[16] *CYP1A2**1F allele is the result of a single nucleotid polymorphism (SNP) (163 C-A) in the intron 1 of the cytochrome P450 CYP1A2 that is associated with increased enzyme inducibility particularly in smokers in comparison to the wild-type allele CYP1A2*1A.[17] It means that clozapine, substrate of CYP1A2, is more readily removed from the body when enzyme is induced. In this report, the patient revealed increased CYP1A2 activity with the genotype of CYP1A2 *1A/*1F. He couldn't attain drug levels in therapeutic range at the standard doses of clozapine because of increased CYP1A2 activity and being a male heavy smoker. İn this case, because of clozapine's increased metabolic clearance and smoking status either increasing dose of clozapine or adding low-dose fluvoxamine (CYP1A2 inhibitor) were recommended.

Risperidone is a prodrug and this atypical antipsychotic primarily metabolized in the liver by CYP2D6 to its active metabolite 9-hydroxy risperidone.[18] The CYP2D6 enzyme activity varies due to over 50 CYP2D6 gene alleles. The poor metabolizer is the most clinically significant phenotype.[15] In this report, the patient is heterozygous for this inactive allele (CYP2D6*5) and his genotype (CYP2D6*1/*5) is indicative of an extensive metabolizer diminished (EMdim), also classified as intermediate metabolizer (IM). This patient couldn't get the desired therapeutic effect at standard doses, because the consequence of risperidone given to an intermediate metabolizer is that not enough of 9-hydroxyrisperidone is produced. The consequence of a prodrug (risperidone) given to an intermediate metabolizer is that not enough of the active drug is

produced. Therefore, instead of risperidone, choosing an alternative antipsychotic which is paliperidone (60% excreted unmetabolized) was recommended for this patient.[10] Because of having *CYP2D6**1/*5 genotype, monitoring plasma concentrations of haloperidol and zuclopenthixol was advised. Dosage adjustments of quetiapine, biperiden and piracetam were not found to be necessary.

Considered the patient's pharmacogenetic test results, probably that, the cause of resistance to treatment of medication were suggested as CYP1A2 ve CYP2D6 enzymes polymorphisms. According to the results of pharmacogenetic tests, the patient was using both antipsychotic drugs could not reach therapeutic range. Ultrarapid CYP1A2 enzyme activity and smoking may have resulted in significant lower clozapine serum concentrations. In addition intermediate CYP2D6 enzyme activity may have been prevented, risperidone converted into its active metabolite 9-hydroxy risperidone. Because clozapine and 9-hydroxy risperidone could not reach serum concentrations, extrapyramidal symptoms may not be observed the patients.

Because we had not detected CYP3A4 enzyme, we could not speculate about serum concentrations of quetiapine (metabolized by CYP2D6, CYP3A4) and haloperidol (metabolized by CYP2D6, CYP3A4). we have assumed that serum concentrations of Zuclopenthixol (metabolized by CYP2D6) is normal. Considering this information, one of the major drawbacks of the present study is lack of measurement of clozapine plasma concentrations.

According to patient's *CYP2C9* genotyping, the patient had *CYP2C9**1/*2 genotype, which is an indicative of the extensive metabolizer diminished (EMdim) phenotype. According to patient's *CYP2C19* results, the patient was found to have CYP2C19 *1/*2 genotype, which is indicative of the extensive metabolizer (EM) phenotype and is associated with normal enzyme activity.

If the patient had been genotyped at the beginning of his antipyschotic therapy, he could have taken therapeutic changes earlier. According to the literature, in particularly cancer, psychiatric disorders, pharmacogenetics has its greatest potential for optimizing the use of drugs with a high rate of failure or adverse outcomes.[19,20] This case report aimed to discuss some of the current opportunities and challenges for implementation of clinical pharmacogenetic testing. This case suggests the clinical usefulness of pharmacogenetic testing in individualized dosage adjustments of antipsychotic medications.

Though not as controversial as predictive genetic testing for later-onset complex diseases, another class of genetic testing that conflict with similar issues of clinical utility and acceptance is pharmacogenetic testing.[21] In the cases of treatment-resistant schizophrenia, pharmacogenetic testing may be advantages in choosing the appropriate dosage and medication.

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