CYP1A2*1F Polymorphism Decreases Clinical Response to Clozapine in Patients with Schizophrenia

Hakan Balibey[1], Cengiz Basoglu[1], Stefan Lundgren[2*], Melih O. Babaoglu[3], Umit Yasar[3], Hasan Herken[4], Anders Rane[2], Atilla Bozkurt[3], Mesut Cetin[1]

ÖZET:

CYP1A2*1F polimorfizmi şizofrenide klozapin tedavisine yanıtı azaltıyor

Giriş: Antipsikotik ilaca yanıt alınamaması ya da tedaviyle ilişkili yan tesirlerin ortaya çıkmasını öngörebilecek sitokrom P450 (CYP) genetik polimorfizmleri bulunmaktadır.

Amaç: Bu çalışmada klozapin tedavisine yanıt ile CYP1A2*1F genetik polimorfizmi arasındaki ilişki araştırılmıştır.

Yöntem: Şizofreni tanısı almış 55 hasta, Kısa Psikiyatrik Değerlendirme Ölçeği (BPRS), Pozitif Belirtileri Değerlendirme Ölçeği (SAPS), Negatif Belirtileri Değerlendirme Ölçeği (SANS), vital bulgular, rutin biyokimyasal incelemelerle değerlendirildi. Olgular 18 hafta süre ile takip edildi. Ölçümler tedavi öncesi ve tedavi sonrası yapıldı. Klozapin 200-600 mg/gün doz aralığında kullanıldı. Daha önceden klozapin kullanan 45 hasta retrospektif olarak değerlendirildi. Onsekizinci hafta sonunda, tedavi öncesine göre BPRS, SANS, SAPS puanlarından birisinde %20'lik azalma tedaviye yanıt kriteri olarak alındı.

Bulgular: Olgular, klozapin başlanmasından 18 hafta sonra tekrar değerlendirildiğinde, tedavinin CYP1A2*1F*1F genotipini taşıyanlarda, en az bir yabanıl tip alel taşıyan bireylere oranla (*1*1 ya da *1*1F) ortalama 2,4 kat daha başarısız olduğu gözlenmiştir (p=0.02). Sigara kullanımı tedaviye cevap oranını %15 oranında anlamlı olarak azaltmıştır (p=0.014).

Sonuç: Özellikle sigara kullanan hastalarda CYP1A2*1F*1F genotipini taşıyor olmak klozapin tedavisinin başarısız olması için bir risk faktörü olabilir.

Anahtar sözcükler: Klozapin, CYP1A2, şizofreni, sigara

ABSTRACT:

CYP1A2*1F polymorphism decreases clinical response to clozapine in patients with schizophrenia

Introduction: Genetic polymorphisms of cytochrome P450 (CYP) may predict the treatment response or occurrence of side effects of antipsychotic drugs.

Aim: We studied the association of response to clozapine treatment in schizophrenic patients in relation to polymorphisms in the CYP1A2 gene.

Methods: The degree of psychosis of the patients (n=55) was assessed using the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS) and routine biochemistry. The patients were monitored for 18 weeks and the scales were applied before starting the treatment and at the end of the follow up period. Clozapine was used at doses of 200 to 600 mg/day. A positive response was defined as a 20% decrease in pre- and post-treatment scores of one of the BPRS, SANS, or SAPS scores. In addition, 45 patients, who were already on clozapine treatment, were assessed retrospectively.

Results: As assessed at the 18th week after start of therapy, lack of response to clozapine treatment was 2.4 fold higher in the patients carrying the CYP1A2*1F*1F genotype (p=0.02) compared to patients carrying at least one wild type allele (i.e. *1/*1 or *1/*1F). Smoking decreased the response rate by about 15% (p=0.014).

Conclusion: The results of our study suggest that the CYP1A2*1F/*1F genotype may be a risk factor for lack of response to clozapine treatment in psychotic patients, especially in cigarette smokers.

Key words: Clozapine, CYP1A2, schizophrenia, smoking

* Stefan Lundgren passed away after completing the study.

[1]Department of Psychiatry, GATA, Istanbul-Turkey
[2]Karolinska Institutet, Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital Huddinge, Stockholm, Sweden
[3]Department of Pharmacology, Faculty of Medicine, Hacettepe University, Ankara-Turkey
[4]Department of Psychiatry, Pamukkale University, Denizli-Turkey

Yazışma Adresi / Address reprint requests to:
Hakan Balibey, MD, Department of Psychiatry, Ankara Military Hospital, Ankara-Turkey

Elektronik posta adresi / E-mail address:
hbalibey@gmail.com

INTRODUCTION

Inter-individual variation in response to antipsychotics is a problem in the treatment of schizophrenia. The pharmacogenetics of drug metabolizing enzymes is a large contributor to this inter-individual variation and polymorphisms of cytochrome P450 (CYP) enzymes have been related to responsiveness to treatment and occurrence of side effects of the drugs used in psychiatric diseases, including psychosis (1,2).

CYP1A2 is responsible for the metabolism of many drugs and procarcinogens (3). Among these drugs, clozapine is metabolized to norclozapine by CYP1A2 (3). The activity of CYP1A2 varies among individuals and the enzyme can be induced or inhibited by other drugs and environmental factors (3,4). In particular, polycyclic

aromatic hydrocarbons, smoking, rifampisin and phenytoin are the main causes of induction of CYP1A2 activity (5,6). Additionally, CYP1A2 is genetically polymorphic and a total of 21 different genetic variants of CYP1A2 have been reported to the CYP Allele Nomenclature Committee (www.cypalleles.ki.se). Among these variants, the substitution of cytosine to adenine at the -163rd (*1F) position has been related to an increased induction rate in subjects who smoke cigarettes (7).

Clozapine is an atypical antipsychotic drug which is effective in 30-60% of schizophrenic patients resistant to common neuroleptics (8-12). It is effective both on the positive and negative symptoms of the disease (13,14). It is also useful in acute psychotic attacks, mania, hypomania, and in some behavioral disorders. However, some patients do not respond to clozapine treatment, and the reason for this resistance to the therapeutic effect has not been fully explained.

Various genetic polymorphisms have been studied in relation to clinical response to clozapine treatment. Clozapine has a high affinity for dopamine and serotonin receptors, and polymorphisms of these receptors have been investigated in patients treated with clozapine (15-22). The association between response to clozapine treatment and polymorphisms of drug metabolizing enzymes has also been studied, but the results are conflicting (23-28). In the present study, we aimed to investigate the association between clinical response to clozapine treatment and CYP1A2*1F genetic polymorphism in Turkish patients with schizophrenia.

PATIENTS and METHODS

Patients

The patients were recruited to the study at the department of psychiatry at GATA Haydarpasa Military Hospital, Istanbul. A total of 100 chronic schizophrenic patients (confirmed with DSM-IV-TR), who were resistant to antipsychotics and who had been treated with clozapine, were included in the study. The protocol of the study was explained to the patients and their caregivers, and informed consent was obtained. The study protocol was approved by the local ethics committee.

The diagnosis was confirmed by at least two psychiatrists. The patients were considered treatment resistant if they were unresponsive to at least three classical antipsychotic drugs from at least two different groups and had been treated for at least 6 weeks with an equivalent dose of chlorpromazine of 1000 mg/day (29). The patients were included in the study if the total score of the Brief Psychiatric Rating Scale (BPRS) was higher than 42, if the patients were 18- to 60-years old, if the number of leucocytes was at least 3500/mm³ and there was no bone marrow abnormality, if no signs or symptoms of any other functional (bipolar disorder, psycho-affective, paranoid disorder) or organic (alcohol, drug, or substance dependence) or psychotic disorder were present, and if there was no contraindication to clozapine use.

Psychiatric Tests

Demographic information (age, gender, marital status, education, and socio-economic status) was collected and clinical characteristics (subtype, onset and duration of the disease and co-administered drugs) of the patients were determined by using the "semi-structured psychiatric conversation form" (SSPCF). The BPRS, developed by Overall and Gorham, and the Scales for the Assessment of Negative (SANS) and Positive (SAPS) Symptoms, developed by Andreasen, were used for the assessment of the severity of symptoms and evaluation of the treatment (30-32).

Clinical Protocol

In the 55 patients, clozapine was started at a dose of 12.5 mg/day and increased by 25 mg increments every other day. The range of final daily doses was 200 mg to 600 mg/day. In 45 patients using clozapine, the BPRS, the SANS and the SAPS scales were completed retrospectively.

For the patients who started clozapine treatment during the course of the study, a complete blood count was performed and the psychiatric scales were applied before starting treatment and at the 18th week of treatment.

Analysis of the CYP1A2*1F:

Allelic discrimination analysis and Taqman® reagents were purchased from Applied Biosystems (Stockholm, Sweden). Genomic DNA was isolated from peripheral venous blood samples using QIAamp DNA isolation kit (Qiagen, Hilden, Germany).

Primers and fluorescence dyed probes were designed by using Primer Express 1.0 software (Applied Biosystems) as summarized in Table 1. Primers and probes were synthesized by Cyber–Gene AB (Novum, Stockholm, Sweden). Allele specific probes were added to the polymerase chain reaction (PCR) mixture which was prepared using a PCR TaqMan Universal PCR Master Mix® in a total volume of 25 μl. This mixture included 0.3 μM sense and antisense primers, 65 pM TET-Probe (6-carboxy-4,7,2',7'- tetrachloro-fluorescein), 50 pM FAM-probe (6-carboxyfluorescein), and an average of 5 ng genomic DNA (33,34). Amplification was carried out with ABI 7700 as follows: one cycle of 50°C for 2 min and 95°C for 10 min, and 35 cycles of 95°C for 15 sec and 60°C for 60 sec. Positive and negative controls were added to each plate.

Table 1: The sequences of primers and probes used in the allelic discrimination of CYP1A2*1F (34).

Primers and probes	Nucleotide sequences
TaqMan probe TET-	5'-CTC TGT GGG CCC AGG ACG CAT-3'
TaqMan probe FAM-	5'-TC TGT GGG CAC AGG ACG CAT GG-3'
TaqMan sense primer	5'-TTT CCA GCT CTC AGA TTC TGT GAT-3'
TaqMan antisense primer	5'-GGA TAC CAG AAA GAC TAA GCT CCA TC-3'
Forward primer*	5'-TTC CCC ATT TTG GAG TGG TC-3'
Reverse primer*	5'-CCG AGA AGG GAA CAG ACT GG-3'

Statistics

The Statistical Package for Social Sciences (SPSS) for Windows (version 10.0) was used for the statistical analysis. Three or more groups were compared using the Kruskal-Wallis test and two groups using the Mann-Whitney U test. The Chi square test was used for comparison of demographic characteristics. The role of socio-demographic and disease dependent factors was evaluated with binary logistic regression analysis. The variables which have statistical significance lower then p<0.20 in univariete logistic regression analysis included in multivariate analysis. "Backward Wald" method was used in this analysis and the first category of independent variables was considered as the reference. A p<0.05 and a 95% confidence interval (CI) were set for the determination of statistical significance.

RESULTS

Three patients were excluded from the study due to severe sedation, akathisia, and refusal of blood sampling

for genotyping. The mean (±SD) age of the patients was 30.5±10.5 (with a range of 19 to 60 years) and the average duration of the disease was 7.1±6.3 years (between 1 and 35 years). The age of onset of the schizophrenia was 23.4±8.2 (between 13 and 55 years). The mean (±SD) clozapine dose was 308±92 mg (between 200 and 600 mg). The socio-demographic characteristics of the patients are summarized in Table 2.

Table 2: The socio-demographic characteristics of the patients.

Variables	Number	%
Marital status		
Married	17	17.5
Unmarried	80	82.5
Education status		
Elementary education	30	30.9
Secondary education	9	9.3
High school	34	35.1
University	24	24.7
Gender		
Male	81	83.5
Female	16	16.5
Schizophrenia family history		
Yes	17	17.5
No	80	82.5
Smoking		
Yes	58	59.8
No	39	40.2

The patients were sub-grouped as paranoid and non-paranoid (a sum of disorganized, unidentified type, and catatonic); 22% were paranoid (n=21) and 78% were non-paranoid (n=76). The numbers of subjects in these groups were insufficient for statistical comparison. The scores of

Table 3: BPRS, SANS, and SAPS scores (mean±standard deviation) of patients at baseline and 18 weeks after clozapine treatment.

Test	Baseline	After treatment
BPRS	57.0±12.6	26.8±17.4
SANS	69.4±32.0	33.8±19.3
SAPS	60.0±16.9	26.1±19.6

Table 4: The association between treatment response (based on 20% improvement in BPRS score) and CYP1A2 genotypes (p=0.02).

CYP1A2 genotypes	Treatment response		Total
	Positive	negative	
*1/*1 + *1/*1F	n=56 (83.6%)	n=11 (16.4%)	n=67 (100%)
*1F/*1F	n=18 (60.0%)	n=12 (40.0%)	n=30 (100%)
Total	n=74 (76.3%)	n=23 (23.7%)	n=97 (100%)

Table 5: Odds Ratios for different variables as determined with binary logistic regression analysis (A). The variables which have statistical significance lower then p<0.20 in univariete logistic regression analysis included in multivariate analysis as adjusted by other variables (B). "R" is reference for the calculation of Odd's ratio.

Variable Characteristics	A Odd's Ratio	95% CI for EXP(B) Lower	95% CI for EXP(B) Upper	p	B Odd's Ratio	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper	p
Gender								
Male	R							
Female	0.692	0.179	2.680	0.594				
Age	1.008	0.965	1.053	0.722				
Smoking								
Absent	R				R			
Present	3.060	1.028	9.112	0.045	3.174	1.031	9.766	0.044
Family history								
Absent	R							
Present	1.012	0.295	3.475	0.985				
Education								
Elementary school	R							
Secondary school	0.344	0.037	3.199	0.348				
High school	0.474	0.136	1.650	0.241				
University	1.650	0.519	5.246	0.396				
Duration of disease								
0-1 years	R							
2-5 years	1.829	0.199	16.773	0.594				
6-10 years	4.000	0.414	38.649	0.231				
11 years and more	3.294	0.345	31.490	0.301				
Type of disease								
Non paranoid	R							
Paranoid	0.655	0.197	2.179	0.490				
Marital status								
Single	R							
Married	1.556	0.405	5.975	0.520				
Genotype								
CYP1A2*1/*1	R				R			
CYP1A2*1F/*1F	4.333	0.825	22.750	0.083	12.144	1.250	117.942	0.031
CYP1A2*1/*1F	1.360	0.260	7.105	0.715	1.539	0.188	12.606	0.688

the psychiatric tests before and after treatment are summarized in Table 3. Most of the patients (76.3%, n =74) responded to the treatment. The response rates among genotype groups are analyzed in Table 4. A positive response rate was significantly lower in patients carrying the *1F/*1F genotype as compared to subjects with at least one wild type allele for CYP1A2.

Furthermore, the effect of socio-demographic factors on drug response was evaluated by considering response rate as the dependent variable and education status, gender, marital status, smoking, subtype of the disease, onset of the disease, duration of the disease, number of hospitalizations and family history as co-variates against genotypes (Table 5). Genotype and smoking significantly affected the response rate (Table 5). It was calculated that

carrying the CYP1A2*1F variant would decrease the treatment response by 1.5 fold and smoking status would decrease it by about 15%).

DISCUSSION

In the present study schizophrenic patients with the CYP1A2*1F variant who smoke cigarettes demonstrated a lower response rate to clozapine treatment after 18 weeks. A 20% decrease in one of the BPRS, SANS or SAPS scores at the end of 18th week has been accepted as a positive treatment response (29). The therapeutic effect of clozapine usually starts in the first week and gradually increases in the following weeks in chronic schizophrenic patients. It has been reported that clinical efficacy is highest during the

3rd and 6th months of the treatment (9-13).

It has been reported that the CYP1A2*1F/*1F genotype leads to an increased CYP1A2 activity by 60-70% compared to a *1/*1F or *1*1 genotype (7). The overall contribution of CYP1A2*1F polymorphism on variability of 1A2 activity in cigarette smokers has been estimated to be 18% (7). In a case study, Ozdemir et al. reported that a patient with a CYP1A2*1F/*1F genotype demonstrated treatment resistance to clozapine (24); in another report, four patients determined as clozapine resistant were also homozygous for the CYP1A2*1F variant (26). Our study confirms the observations in these case reports, and demonstrates the impact of the CYP1A2*1F variant on the outcome of clozapine treatment.

In our study, we found that treatment response was significant in the 12th week of the treatment. At the end of the 18th week mean BPRS score was 53% lower considering all patients. The scores of other clinical tests also decreased to a similar degree. Overall, about 3/4 of the patients were found to be responders to the treatment. Clozapine has been reported to be effective in about 30-60% of schizophrenic patients resistant to other antipsychotics and these constitute about 20% of the whole patient population. Response to pharmacotherapy in this patient group depends on many socio-demographic and clinical factors. In our study, we did not observe any effect of gender and subtype, onset, or duration of the disease. Lieberman et al. showed that female gender and early onset of the disease have a negative effect on the therapeutic effect of the treatment (8).

The frequency of the CYP1A2*1F variant has been reported in different ethnic groups (3,7,35). The distribution of this variant in the present patient population from Turkey is similar to that of other Caucasian populations. CYP1A2 has an important role in the metabolism of clozapine (24-27,36). Ozdemir et al. suggests that CYP1A2*1F genetic polymorphism might be related to increased enzyme activity resulting in subtherapeutic concentrations of the drug and resistance to the treatment (24). Due to the large inter-individual variation, the association has not been clearly identified. Studies on multiple genetic loci related to the pharmacodynamic characteristics of clozapine have suggested that other genetic variables also contribute to explaining the variation (2). Therefore, other genetic factors should also be taken into account.

Bertilson et al. reports a strong association between CYP1A2 activity and plasma clozapine concentrations after intake of a single oral dose of the drug in healthy volunteers (36). It may therefore be hypothesized that clinical response to clozapine treatment is related to plasma concentrations of clozapine (36,37). However, in another study which included 58 schizophrenic patients, CYP1A2 *1F, *1C and *1D genotypes were not correlated with clozapine serum concentrations after correction for the dose and weight or concentration/dosage ratios (25).

Clinical studies suggest a therapeutic window of 200-600 $\mu g/l$ of clozapine for an optimal response. Levels of clozapine higher than this range seem to be associated with side effects and lower concentrations with lower clinical response (8-10,38). Both clozapine and norclozapine concentrations have been reported to be lower in cigarette smokers compared to nonsmokers (34,38). Considering this information, one of the major drawbacks of the present study is lack of measurement of clozapine plasma concentrations.

In conclusion, CYP1A2*1F polymorphism and smoking are significant determinants of the success of clozapine treatment whereas gender, subtype of the disease, onset of the disease, and marital status do not seem to influence clozapine response in schizophrenic patients. Determination of CYP1A2*1F polymorphism may be helpful in predicting treatment response especially in smoking psychotic patients.

References:

1. Fleeman N, McLeod C, Bagust A, Beale S, Boland A, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. Health Technol Assess. 2010;14(3):1-157.

2. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol Psychiatry 2007;12(8):707-47.

Klinik Psikofarmakoloji Bülteni, Cilt: 21, Sayı: 2, 2011 / Bulletin of Clinical Psychopharmacology, Vol: 21, N.: 2, 2011 - www.psikofarmakoloji.org

97

3. Zhou SF, Wang B, Yang LP, Liu JP. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. Drug Metab Rev 2010;42(2):268-354.

4. Zhou SF, Yang LP, Zhou ZW, Liu YH, Chan E. Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2. AAPS J. 2009;11(3):481-94.

5. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev 1997; 29(1-2):413-580.

6. Lin JH, Lu AY. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 1998; 35(5):361-90.

7. Sachse C, Brockmoller J, Bauer S, Roots I. Functional significance of a C-->A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 1999; 47(4):445-9.

8. Lieberman JA, Safferman AZ, Pollack S, Szymanski S, Johns C, Howard A, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994; 151(12):1744-52.

9. Lindstrom LH. The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. Acta Psychiatr Scand 1988; 77(5):524-9.

10. Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, et al. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2010;(11):CD006633.

11. Uzun O, Ozsahin A, Ozmenler KN, Doruk A, Battal S. Clozapine in treatment-resistant schizophrenia: Followed-up study for three years. Klinik Psikofarmakoloji Bulteni -Bulletin of Clinical Psychopharmacology 2000; 10(2):74-80.

12. Citak S, Cakici ET, Cakici M. Neuropsychological assessment in schizophrenic patients treated with haloperidol or clozapine. Klinik Psikofarmakoloji Bulteni -Bulletin of Clinical Psychopharmacology 2000; 19(1):5-14.

13. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151(1):20-6.

14. Carpenter WT, Jr., Conley RR, Buchanan RW, Breier A, Tamminga CA. Patient response and resource management: another view of clozapine treatment of schizophrenia. Am J Psychiatry 1995; 152(6):827-32.

15. Xu M, Xing Q, Li S, Zheng Y, Wu S, Gao R, et al. Pharacogenetic effects of dopamine transporter gene polymorphisms on response to chlorpromazine and clozapine and on extrapyramidal syndrome in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34(6):1026-32.

16. Melkersson KI, Gunes A, Dahl ML. Impact of serotonin receptor 2A gene haplotypes on C-peptide levels in clozapine- and olanzapine-treated patients. Hum Psychopharmacol 2010; 25(4):347-52.

17. Souza RP, de Luca V, Meltzer HY, Lieberman JA, Kennedy JL. Influence of serotonin 3A and 3B receptor genes on clozapine treatment response in schizophrenia. Pharmacogenet Genomics 2010; 20: 274-6.

18. Hwang R, Zai C, Tiwari A, Muller DJ, Arranz MJ, Morris AG, et al. Effect of dopamine D3 receptor gene polymorphisms and clozapine treatment response: exploratory analysis of nine polymorphisms and meta-analysis of the Ser9Gly variant. Pharmacogenomics J 2010; 10: 200-18.

19. Souza RP, Tampakeras M, Basile V, Shinkai T, Rosa DV, Potkin S, et al. Lack of association of GPX1 and MnSOD genes with symptom severity and response to clozapine treatment in schizophrenia subjects. Hum Psychopharmacol 2009; 24(8):676-9.

20. Consoli G, Lastella M, Ciapparelli A, Catena Dell'Osso M, Ciofi L, Guidotti E, et al. ABCB1 polymorphisms are associated with clozapine plasma levels in psychotic patients. Pharmacogenomics 2009; 10(8):1267-76.

21. Kohlrausch FB, Salatino-Oliveira A, Gama CS, Lobato MI, Belmonte-de-Abreu P, Hutz MH. G-protein gene 825C > T polymorphism is associated with response to clozapine in Brazilian schizophrenics. Pharmacogenomics 2008; 9(10):1429-36.

22. Barlas IO, Cetin M, Erdal ME, Semiz UB, Basoglu C, Ay ME, et al. Lack of Association Between DRD3 Gene Polymorphism and Response to Clozapine in Turkish Schizoprenia Patients. Am J Med Genet B 2009; 150B(1):56-60.

23. Arranz MJ, Dawson E, Shaikh S, Sham P, Sharma T, Aitchison K, et al. Cytochrome P4502D6 genotype does not determine response to clozapine. Br J Clin Pharmacol 1995; 39(4):417-20.

24. Ozdemir V, Kalow W, Okey AB, Lam MSM, Albers LJ, Reist C, et al. Treatment-resistance to clozapine in association with ultrarapid CYP1A2 activity and the C -> A polymorphism in intron 1 of the CYP1A2 gene: Effect of grapefruit juice and low-dose fluvoxamine. J Clin Psychopharm 2001; 21(6):603-7.

25. Kootstra-Ros JE, Smallegoor W, van der Weide J. The cytochrome P450 CYP1A2 genetic polymorphisms *1F and *1D do not affect clozapine clearance in a group of schizophrenic patients. Ann Clin Biochem 2005; 42(Pt 3):216-9.

26. Eap CB, Bender S, Jaquenoud Sirot E, Cucchia G, Jonzier-Perey M, Baumann P, et al. Nonresponse to clozapine and ultrarapid CYP1A2 activity: clinical data and analysis of CYP1A2 gene. J Clin Psychopharmacol 2004; 24(2):214-9.

27. van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003; 13(3):169-72.

28. Sirot EJ, Knezevic B, Morena GP, Harenberg S, Oneda B, Crettol S, et al. ABCB1 and Cytochrome P450 Polymorphisms Clinical Pharmacogenetics of Clozapine. J Clin Psychopharm 2009; 29(4):319-26.

29. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the Treatment-Resistant Schizophrenic - a Double-Blind Comparison with Chlorpromazine. Arch Gen Psychiat 1988; 45(9):789-96.

30. Overall JE, Gorham DR. The Brief Psychiatric Rating-Scale. Psychol Rep 1962; 10(2):799-812.

31. Andreasen NC, Flaum M, Swayze VW, Tyrrell G, Arndt S. Positive and Negative Symptoms in Schizophrenia - a Critical Reappraisal. Arch Gen Psychiat 1990; 47(7):615-21.

98

Klinik Psikofarmakoloji Bülteni, Cilt: 21, Sayı: 2, 2011 / Bulletin of Clinical Psychopharmacology, Vol: 21, N.: 2, 2011 - www.psikofarmakoloji.org

32. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry Suppl 1989: (7):49-58.

33. Livak KJ. Allelic discrimination using fluorogenic probes and the 5' nuclease assay. Genet Anal 1999; 14(5-6):143-9.

34. Nordmark A, Lundgren S, Ask B, Granath F, Rane A. The effect of the CYP1A2 *1F mutation on CYP1A2 inducibility in pregnant women. Br J Clin Pharmacol 2002; 54(5):504-10.

35. Schulze TG, Schumacher J, Muller DJ, Krauss H, Alfter D, Maroldt A, et al. Lack of association between a functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene and tardive dyskinesia in schizophrenia. Am J Med Genet 2001; 105(6):498-501.

36. Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1994; 38(5):471-3.

37. Buur-Rasmussen B, Brosen K. Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. Eur Neuropsychopharmacol 1999; 9(6):453-9.

38. Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993; 13(6):383-90.

Klinik Psikofarmakoloji Bülteni, Cilt: 21, Sayı: 2, 2011 / Bulletin of Clinical Psychopharmacology, Vol: 21, N.: 2, 2011 - www.psikofarmakoloji.org

99