THE RESPONSE TO ATYPICAL ANTIPSYCHOTIC DRUGS IN CORRELATION WITH THE CYP2D6 GENOTYPE: CLINICAL IMPLICATIONS AND PERSPECTIVES

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Abstract

Atypical antipsychotics are widely used and have been shown to be effective against both positive and negative symptoms of schizophrenia. Through this study we intended to bring to the forefront attention the implications of pharmacogenetics for obtaining the optimum results after antipsychotic treatment in a very sensitive category of patients: children and adolescents. This study was performed between 2009 and 2013 and includes children and adolescents with a diagnosis of schizophrenia or bipolar disorder. 81 patients, aged between 9 and 20 years were included in this study (median age was 15.74±4). The efficacy of the therapy was evaluated through the mean change in the PANSS total scores from baseline- T0, through every timepoint - T1=after 3 months, T2=after 6 months, T3=after 12 months, till endpoint - T4=after 18 months. Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination. Our results, showing statistically significant differences of the clinical score between the groups classified based on the genotype, sustain the use of the pharmacogenetic screening in clinical practice for the personalization of the therapy.

Rezumat

Antipsihoticele atipice, sunt utilizate pe scară largă și s-au dovedit a fi eficiente împotriva simptomelor pozitive și negative ale schizofreniei. Prin acest studiu am dorit să aducem în prim plan implicațiile farmacogeneticii pentru obținerea rezultatelor optime după

tratamentul antipsihotic într-o categorie foarte sensibilă de pacienți: copii și adolescenți. Acest studiu a fost realizat între 2009 și 2013 și include copii și adolescenți cu diagnostic de schizofrenie sau de tulburare bipolară. 81 de pacienți, cu vârste cuprinse între 9 și 20 ani, au fost incluși în acest studiu (vârsta medie a fost de 15,74 ± 4). Eficacitatea terapiei a fost evaluată prin înregistrarea modificării scorurilor PANSS medii de la momentul initial (înaintea începerii terapiei)-T0, la diferite moment de timp - T1 = după 3 luni, T2 = după 6 luni, T3 = dupa 12 luni, până la punctul final - T4 = după 18 luni. Genotipurile au fost determinate prin măsurarea specifică a fluorescenței utilizând *software*-ul pentru discriminare alelică. Rezultatele noastre, care arată diferențe semnificative statistic ale scorului clinic între grupurile clasificate pe baza genotipului, susțin utilizarea *screening*-ului farmacogenetic în practica clinică pentru personalizarea terapiei.

Keywords: atypical antipsychotics, CYP2D6 genotype, PANSS score

Introduction

The pharmacogenetic studies allow understanding the role of the genetic component in the response to a particular drug and determining optimal doses for each patient, an important factor in personalized medicine [5, 24, 28]. Today, atypical antipsychotics represent the election treatment for patients diagnosed with schizophrenia or bipolar disorder, being widely used and proving to be effective against both positive and negative symptoms of schizophrenia. There are different Single Nucleotide Polymorphisms that were found to be correlated with the clinical evolution in patients that undergo atypical antipsychotic treatment [1, 2, 12, 14, 15, 28]. It is also well known today, with the development of pharmacogenetics, that the genetic variability can affect both pharmacokinetic and pharmacodynamic drug properties [1, 3, 5, 6, 8, 17, 19, 22, 24]. The variability in the response to atypical antipsychotic drugs could be significantly related to the drug metabolism polymorphisms [29]. Cytochrome P450 (CYP450) enzymes are significantly involved in the metabolism of many categories of psychiatric drugs, especially the cytochrome P450 2D6 (CYP2D6) being correlated with the drug metabolism and response to some atypical antipsychotics [7, 11, 13, 17, 24]. CYP2D6 genotyping allows the personalization of the therapy based on the particular genetic pattern of each individual [12, 16, 17, 24, 26]. The key CYP2D6 metabolized atypical antipsychotics are risperidone and aripiprazole [3, 6, 10, 11]. Based on the CYP2D6 genotype, four types of metabolizer phenotypes were identified: ultra-rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) [18]. The poor metabolizers may have side effects from usual doses of some atypical antipsychotics (risperidone, aripiprazole) but they would not be expected to have poor response and adverse reactions to

other atypical antipsychotics, like clozapine, quetiapine or ziprasidone [3, 18]. The ultrarapid metabolizers may not have a drug response as expected, experiencing a lack of clinical efficacy to usual doses of antipsychotics [29].

In this context, the pharmacogenetics of the drug response to atypical antipsychotics represents a promising perspective in tailoring the individualized treatment to the needs of the patient and avoiding the lack of clinical response efficacy, as well as the significant side effects [4, 5, 20, 28]. Especially within paediatric population, who appears to be at greater risk because of the metabolic particularities and other factors, these pharmacogenetic aspects should be addressed with great attention [16, 23, 25, 27]. Through this study we intended to bring to the forefront attention the implications of pharmacogenetics for obtaining the optimum results after antipsychotic treatment in a very sensitive category of patients: children and adolescents [27].

Materials and Methods

This study was performed between 2009 and 2013 and includes children and adolescents with a diagnosis of schizophrenia or bipolar disorder. Enrolment of patients was done at the University Hospital for Child and Adolescent Psychiatry and Neurology Timisoara. The inclusion criteria in this study were: inpatients or outpatients, male and female, with a current diagnosis of schizophrenia or bipolar disorder, according to Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM IV) and reconfirmed by a Child and Adolescent Psychiatrist through K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version); the age <18 years or under 21 years if the patients were still studying in school; patients undergoing treatment with the following atypical antipsychotics – Risperidone, Aripiprazole or Olanzapine; a baseline PANSS (Positive and Negative Syndrome Scale) score ≥ 70. We obtained for each patient under 18 years, the informed consent from the parents/legal guardians and the assent from the child and for the patients over 18 years we obtained the informed consent signed by them. Our study is in accordance with the Ethical Committee regulations of the University of Medicine and Pharmacy 'Victor Babes' Timisoara and with the ICH-GCP (Good Clinical Practice) regulations and guidelines.

81 patients, aged between 9 and 20 years were included in this study (median age was 15.74±4). The sex ratio in the study lot was 1.17/1 females (44) to males (37).

Clinical evaluation of the patients and the PANSS assessment

The PANSS-Positive and Negative Syndrome Scale was applied by an authorized rater, in order to offer an objective measure for the psychiatric

symptoms, to evaluate the psychopathology, the positive, negative and general symptoms. In their psychiatric history, some of the patients have changed their treatment through switching between different antipsychotics, atypical or typical, sometimes because of the lack of efficacy or because of the adverse events. We assessed the drug response through the efficacy of the atypical antipsychotic pharmacologic treatment and the clinical outcome, measured through the PANSS scores. The efficacy of the pharmacotherapy was evaluated through the mean change in the PANSS total scores from baseline- T0, through every timepoint - T1=after 3 months, T2=after 6 months, T3=after 12 months, till endpoint - T4=after 18 months. We took into account the fact that high PANSS scores mean a poor clinical evolution in schizophrenia and bipolar disorder and decreased scores are correlated with a clinical improvement. We quantified a good drug response if an improvement with ≥30% of the PANSS score from baseline was noted.

CYP2D6 genotyping

CYP2D6 genotyping was performed using Reverse transcription-polymerase chain reaction (RT-PCR). Genomic DNA isolation from blood collected on EDTA as anticoagulant was performed by using QIAamp DNA Mini Kit (Qiagen, Germany). DNA samples were stored at -80°C. The CYP2D6 genotyping was performed after enrollment of the last patient, and the laboratory staff was blinded to the patients' data. CYP2D6 variant identification was carried out on a 7900HT Fast Real-Time PCR instrument (Applied Biosystems, Foster City, CA) by using TaqMan Drug Metabolism Genotyping Assay for Allelic Discrimination C__27102431_D0 (CYP2D6*4, 1846G>A), TaqMan® PCR Master Mix and DNA probe according to the protocol provided by the producer. Two controls were used: AL-1 corresponding to the wild-type (wild-type) was VIC dye-labeled and AL-2 (CYP2D6*4) corresponding to the mutant type (*4) was fluorescein FAM dye-labeled. Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination (Applied Biosystems, Foster City, CA).

In this study we focused on CYP2D6*4 allele identification because it is the most frequent variant in the Caucasian population, responsible for a poor metabolizer phenotype. We classified the patients included in this study in three groups based on the genotype identified. Group 1 of patients included subjects that exhibit the presence of AL- 2 (*4) and were not carrying the functional allele AL-1 (wt). In group 2 were included 25 subjects carrying one functional (wt) and one non-functional allele (*4). Group 3 was the most numerous group including 53 subjects carrying the functional allele AL-1 (wt) and missing the non-functional allele AL-2 (*4).

Statistical analysis

All analyses were carried out using SPSS software (version 17.0, Chicago, IL, USA) and Microsoft Excel. For comparing the PANSS scores at different time points, the Friedman non-parametric test for pair values was used. For comparing the clinical response between groups, the Mann-Whitney non-parametric test was applied. For comparing the mean total PANSS scores at two different time points, the nonparametric test Wilcoxon signed Ranks was used.

Results and Discussion

For the schizophrenia lot, at baseline, the total mean PANSS score was 89.03 ± 19.1, the positive symptoms score 23.8±6.5 and the negative symptoms score 20.02±8.8. We applied Friedman nonparametric test for pair values in order to compare the PANSS mean total scores values for 5 time points (T0=Baseline, T1=after 3 months, T2=after 6 months, T3=after 12 months, T4=after 18 months), for the 3 genotype groups identified, in the whole sample of patients with schizophrenia and bipolar disorder (Table I).

Table I.

Comparison between the mean total PANSS scores for the 5 time points for the 3 genotype-groups

Time point	No. cases	PANSS Mean	Std. Deviation	Minimum	Maximum
Group 1					
T0	3	157.7	56.89	92	192
T1	3	153.3	55.72	89	186
T2	3	149.3	54.86	86	182
T3	3	140.0	54.95	77	178
T4	3	137.3	55.29	74	176
Group 2					
T0	25	130.4	35.19	84	197
T1	25	122.2	32.62	79	185
T2	25	115.4	30.37	76	180
T3	25	110.9	30.84	65	190
T4	25	106.2	26.14	62	168
Group 3					
T0	53	117.2	28.16	76	185
T1	53	103.4	23.60	72	176
T2	53	90.8	19.40	62	140
T3	53	79.8	14.48	55	125
T4	53	69.7	12.29	48	95

We have obtained statistical significant differences for group 2 and 3, between the 5 time points, concerning the PANSS scores ($p<0.001$, the

significance level α=0.001). The PANSS mean total scores registered a statistically significant decrease, meaning an improvement concerning the clinical outcome especially for the patients in group 3. Comparing the total PANSS scores for group 3 in each 2 with 2 time points with the Wilcoxon signed Ranks non parametric test, we obtained statistically significant differences, the p values appearing in Table II.

Table II.

Comparison of the total PANSS scores in group 3 for each 2 with 2 time points

Comparison	$p^{significance}$	α level of significance
PANSS T1 - PANSS T0	<0.001[s]	0.001
PANSS T2 - PANSS T0	<0.001[s]	0.001
PANSS T3 - PANSS T0	<0.001[s]	0.001
PANSS T4 - PANSS T0	<0.001[s]	0.001
PANSS T2 - PANSS T1	<0.001[s]	0.001
PANSS T3 - PANSS T1	<0.001[s]	0.001
PANSS T4 - PANSS T1	<0.001[s]	0.001
PANSS T3 - PANSS T2	0.015[s]	0.05
PANSS T4 - PANSS T2	0.001[s]	0.01
PANSS T4 - PANSS T3	0.003[s]	0.01

For group 1 the differences between the PANSS scores for the 5 time points were not statistically significant (p=0.109, α=0.05), meaning that the patients in this group didn't register an improvement concerning the clinical evolution. The decrease of the PANSS scores values from baseline to T4 was statistically significant in group 3, with a significance threshold of α=0.001 for the comparisons T0-T1-T2, with α=0.01 for the comparison T3-T4 and α=0.05 for T2-T3. This fact means that in the group 3, the patients registered a statistically significant decrease of the PANSS mean total scores, correlated with the clinical improvement as a positive response to the atypical antipsychotic drugs. For each of the genotype groups a decrease of the mean total PANSS scores was found (Figure 1) indicating an amelioration of the symptoms and a clinical improvement.

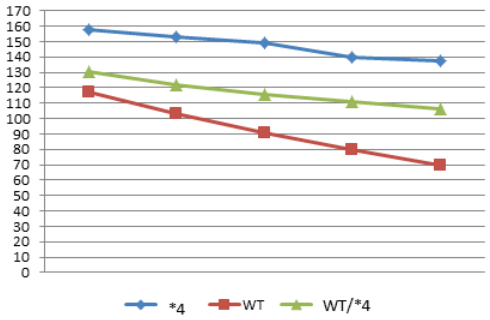

Figure 1.
PANSS scores evolution for the 3 genotypes from T0-T4

The mean total PANSS scores registered a significant decrease in the group 3, meaning that a clinical improvement correlated with a good drug response was noticed for these patients (WT).

We compared the differences between group 2 and group 3 regarding the PANSS score for each time point (Table III). We noticed that for the group 2 the PANSS score was higher than for group 3 for each time point, meaning that the patients with the WT/*4 genotype didn't exhibit an efficient drug response, expressed through the high PANSS scores, correlated with a poor clinical evolution.

Table III.
Comparison of the PANSS scores for the genotype-group 2 and 3 for each time point

Time point	Genotype	No. cases	PANSS Mean	Std. Deviation	Std. Error Mean
T0	WT	53	117.2	28.16	3.87
	WT/*4	25	130.4	35.19	7.04
T1	WT	53	103.4	23.60	3.24
	WT/*4	25	122.2	32.62	6.52
T2	WT	53	90.8	19.40	2.67
	WT/*4	25	115.4	30.37	6.07
T3	WT	53	79.8	14.48	1.99
	WT/*4	25	110.9	30.84	6.17
T4	WT	53	69.7	12.29	1.69
	WT/*4	25	106.2	26.14	5.23

The differences between the mean total PANSS scores at To-baseline were found to be statistically non-significant, while at time points T1, T2, T3 and T4, the differences were statistically significant (Table IV), indicating a better clinical evolution for the patients who did not exhibit *4 allele in their genotype.

Table IV.

The statistical significance of the comparison between the genotype group 2 and 3 for each time point

PANSS time point	p ^{significance}	α level of significance
T0	0.080^{ns}	0.05
T1	0.005^{s}	0.01
T2	0.001^{s}	0.01
T3	$<0.001^{s}$	0.001
T4	$<0.001^{s}$	0.001

We found significant correlations between the WT/*4 genotype, higher PANSS scores, a poor clinical outcome and a bad drug response to the atypical antipsychotics (p =0.001).

In our study lot, we found for the group 3 a good drug response, with a decrease ≥ 30% in the PANSS scores from baseline. The patients from group 1 and 2 didn't achieve a decrease ≥ 30% in the PANSS scores, meaning these patients didn't register a good drug response to the atypical antipsychotics.

Concerning the clinical drug response to the atypical antipsychotics, we found statistically significant differences between the CYP2D6 genotype groups. The response to atypical antipsychotics varies widely between patients and this response is not completely predicted by the dose administered [29]. The drug response to atypical antipsychotics is correlated with the CYP2D6 genotype, the polymorphisms of the CYP2D6 influencing the medication efficacy and the clinical evolution [6, 8, 9, 10].

The pharmacogenetics and pharmacokinetic of atypical antipsychotics have been evaluated in some studies in adults, but there is a scarcity of research studies involving children and adolescents, although these medication is extensively used in this population [7]. The pharmacokinetics of risperidone and aripiprazole are not affected by age, but its half-life varies depending on the activity of the CYP2D6 enzyme [8, 12, 13]. There is a substantial phenotypical difference between patients carrying 1 functional allele (wt) and 1 nonfunctional allele (*3, *4, *5) and the patients exhibiting 2 CYP2D6 variant alleles (2 reduced-function or 1 reduced-function in combination with a nonfunctional variant alleles) [3, 10, 11]. In the same time, there are few data regarding the impact of *CYP2D6* isoenzyme polymorphisms on the long-term evolution of the patients using atypical antipsychotic drugs. In this context, our research is valuable, because the study period is long enough to follow different clinical issues in correlation with the drug response.

The paediatric patients, being in development, the whole trajectory of their future could be compromised because of the lack of efficacy or a poor drug response to the atypical antipsychotics. For this category, in particular, the drug safety issues are crucial, so that studying the underlying genetic mechanisms of adverse drug reactions can bring important benefits to patients by helping in the process of choosing the best drug with the least expected side effects [14, 16, 21, 23, 25].

In our research, the patients from the group 1 and 2 could be considered as non-responders, because of the lack of efficacy and a poor drug response. This poor drug response to the atypical antipsychotics in correlation with the CYP2D6 polymorphism could explain, why a lot of psychotic patients are treatment-resistant or clinically nonresponsive [16, 26]. The pharmacogenetics is a future perspective for the usual clinical practice because an individualized, personalized, tailored treatment be preferred. This is also an important ethical issue for the patients, especially for children and adolescents, because instead of permanently switching antipsychotics is much more efficient to apply targeted pharmacotherapy and interventions [4, 5, 9, 12, 14, 21].

CYP2D6 genotype could help the clinician choose an antipsychotic from the category that is not CYP2D6 metabolized (clozapine, quetiapine or ziprasidone) or if they encounter severe side effects (metabolic, hormonal, weight gain) metformin could be prescribed beside the atypical antipsychotics [4, 25, 29].

In the case of children with schizophrenia and bipolar disorder, even more attention and care should be paid, when choosing the antipsychotics. It is important to note the fact that the poor drug response, the lack of efficacy brings with it non-compliance to therapy [21, 27, 28].

Nowadays, we step in the era of personalized medicine, a medicine based on the individual genetic pattern and the focus is on revealing the mechanism that could explain the individual variability in drug response and on the identification of pharmacokinetic and pharmacodynamic biomarkers, useful in the clinical practice [5, 29].

Conclusions

We can conclude that in this study, the CYP2D6 genotype was a useful tool for the prediction of the clinical evolution after administration of atypical antipsychotics.

Our results, showing statistically significant differences of the clinical score between the groups classified based on the genotype, sustain

the use of the pharmacogenetic screening in clinical practice for personalization of the therapy.

As future perspective, CYP2D6 pre-screening should be performed before prescribing the atypical antipsychotics. The CYP2D6 genotype proved to be a significant predictor of the clinical outcome, proving to be a target for further research and analyses. Through proper intervention strategies the quality of life (QOL) of the patients and their families can be improved, as well as the prognostic of patients with psychosis.

We achieved new perspectives, through new diagnostic and monitoring methods, through the implementation of a complex model of pharmacotherapy and intervention strategies.

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