Original Article

A Preliminary Study of Genetic Polymorphisms Potentially Related to the Adverse Effects of Aripiprazole

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Abstract

Aripiprazole is an atypical antipsychotic drug that is mainly transformed by the hepatic enzymes CYP2D6 and CYP3A4. Dose adjustment is recommended for CYP2D6-poor metabolizers. Aripiprazole is generally well tolerated by most adult patients, but occasionally adverse effects can occur in some individuals resulting in the drug being withdrawn. Recent studies suggested that other genes involved in drug metabolism, transport, and elimination can be related to the efficacy and safety of drug therapy. This study aimed to evaluate the differences in genetic variants between patients who tolerated the therapy well and those who experienced adverse effects leading to withdrawing the drug. The genetic profiling of 20 genes was performed using MassARRAY technology. No differences between both groups in the *ABCB1*, *COMT*, *CYP2D6*, *CYP3A4*, and *CYP3A5* polymorphisms were found. Unexpectedly, we observed a higher frequency of homozygous *CYP1A21F/*1F* (78% *vs.* 45%) and *CYP2B6*1/*1* (80% *vs.* 45%) as well as the frequency of CYP1A2 ultra-rapid metabolizes in the group with adverse effects. Moreover, a combined homozygous status (*CYP1A2*1F/*1F/ CYP2B6*1/*1*) has been exclusively identified in patients with adverse effects. To date, there are no findings about the possible role of CYP1A2 and CYP2B6 enzymes in aripiprazole metabolism. Thus, our preliminary data suggest that the *CYP1A2*F* and/or *CYP2B6*1* alleles may contribute to the adverse effects of aripiprazole. Therefore, further studies on larger sample sizes are needed to confirm our findings.

Keywords: Aripiprazole, Adverse drug effect, Cytochrome P450, Pharmacogenetics, Phenotype, SNP polymorphisms

Introduction

Aripiprazole (ARI) is used in the treatment of various psychotic disorders, such as schizophrenia, bipolar disorder, major depression, or irritability associated with autistic disorder. ARI is an atypical antipsychotic, referred to as a third-generation drug [1]. It binds to multiple receptors, but exhibits remarkably high affinity for D2, D3, 5-HT1A, and 5-HT2A receptors. The characteristic of ARI that distinguishes it from other antipsychotics is its partial agonism towards dopamine receptors (D2 and D3) and serotonin receptors (5-HT1A and 5-HT2C) [2, 3]. The pharmacokinetics of ARI is mediated predominantly by CYP2D6 and CYP3A4 enzymes, less significantly by CYP3A5 enzyme and ACBC1 transporter [4, 5]. The parent drug is metabolized into an active metabolite dehydro-aripiprazole (D-ARI). The Food and Drug Administration (FDA) recommends dose adjustment according to the genetically predicted metabolic status of CYP2D6 to improve the drug's response [6]. Half of the regular dose is recommended for CYP2D6 poor metabolizers (PMs) or even a quarter of the regular dose for CYP2D6 PM who simultaneously take any strong CYP3A4 inhibitors for more than 14 days. Other factors such as gender, age, or smoking have no significant effect on the pharmacokinetics of ARI (EMEA/H/C/002755/0000).

ARI is effective and well tolerated in most patients with schizophrenia, bipolar disorder, and autism spectrum in comparison to other antipsychotics. However, in some patients, adverse effects during ARI treatment including somnolence, sedation fatigue, concentration difficulties, restlessness, akathisia, and tardive dyskinesia can be noticed [7]. In some patients, aripiprazole may lead to weight gain, but metabolic parameters, including overall glucose and lipids, are not significantly altered [8].

Several studies suggested that polymorphisms in other genes, such as *ABCB1*, *DRD2*, and *5-HTRs* genes can be

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related to ARI response and adverse effects during drug therapy [5, 9, 10]. Although ARI is not a substrate for the enzymes CYP1A2 and CYP2B6, results from a study by Koller *et al*. showed that polymorphism in the *CYP1A2* gene can influence the pharmacokinetics of ARI and D-ARI as well as CYP1A2 phenotype can be related to adverse effects of the drug [11]. Interestingly, the CYP2B6 enzyme, similar to CYP1A2, is expressed in the brain and also may contribute to the metabolism of CNS-acting drugs and neurological side effects of certain medications [12]. However, to date, the role of CYP1A2 and/or CYP2B6 enzymes in the metabolism of ARI has not been established.

The present study aimed to determine if differences exist in the distribution of polymorphic variants of genes involved in drug metabolism, transport, and mechanism of action between patients with aripiprazole monotherapy and patients who experienced adverse drug effects.

Materials and Methods

Patients

Nineteen patients (9 men and 10 women) of Caucasian origin were enrolled in the study. Patients were predominantly diagnosed with schizophrenia (77%), and a smaller percentage were affected by personality disorder (13%) and bipolar disorder (10%). All patients were recruited from Babinski University Hospital (Krakow, Poland). Informed consent was obtained from all subjects before inclusion in the study. Inclusion criteria were as follows: (1) aripiprazole (ARI) therapy (ongoing or withdrawn), and (2) age 18 to 60 years. Exclusion criteria were as follows: (1) polypharmacy with drugs listed as CYP2D6 inhibitors or CYP3A4 inducers or inhibitors, (2) organic lesions of the central nervous system, and (3) mental retardation. Patients were divided into two subgroups: the first ARI group received only ARI, and the second ARI-ADE group was previously treated with ARI but due to adverse drug effects ARI was withdrawn.

Genotyping

DNA was extracted from 200 µl of whole blood using QIAamp DNA Blood Mini Kit (Qiagen). The quantity was assessed spectrophotometrically in a NanoDrop One (Thermo Scientific) and quality was by agarose gel electrophoresis. Additionally DNA quantification was carried out using a Qubit dsDNA BR assay kit (Invitrogen, Thermo Scientific) and Invitrogen Qubit™ 3.0 Fluorometer (Thermo Scientific) following the manufacturer's protocol. All patients were genotyped for 68 SNPs/INDELs across 20 genes, plus 5 CNV targets in *CYP2D6* included in the Agena VeriDose Core panel and hybrid *CYP2D6* alleles included in the Agena VeriDose CYP2D6 CNV Panel using MassArray® System (Agena Bioscience).

Translation of Genotype into Phenotype

To simplify the *CYP2D6* and *CYP1A2* genotypes interpretation the calculation of activity score (AS), based on the functionality of the alleles, was applied. Each *CYP2D6* allele is assigned a value of 0 (no-function allele), 0.25 or 0.5 (decreased-function allele), or 1 (normal function allele). The sum of the values provides the AS of a genotype. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, the following phenotypes are distinguished: poor metabolizer (PM) when AS=0, intermediate metabolizer (IM) when AS >0 and ≤1.25, normal metabolizer (NM) when AS >1.25 and ≤ 2.25, and ultra-rapid metabolizer (UM) when AS >2.25.

The following value was assigned to *CYP1A2* alleles based on their functionality: 0.5 to *1C, 1 to *1, 1.25 to *1B, and 1.5 to *1F [13]. CYP1A2 phenotypes were predicted based on the sum of functionality values: PM 1-1.5; NM 1.75-2.5; UM 2.75-3 [14].

CYP3A4 and *CYP3A5* genotypes are merged into a CYP3A phenotype. The star alleles were defined as normal alleles (*CYP3A4*1* and *CYP3A5**1), decreased activity one allele *(CYP3A4*22*), and no activity one allele (*CYP3A5*3*). The following phenotypes were determined based on genotype clusters: PM for *CYP3A4*22/*22* or *CYP3A4*1/*22* and *CYP3A5*3/*3* cluster; IM for *CYP3A4*1/*1* and *CYP3A5*3/*3*; IM for *CYP3A4*22/*22* or *CYP3A4*1/*22* and *CYP3A5*1/*1* or *CYP3A5*1/*3*; NM for *CYP3A4*1/*1* and *CYP3A5*1/*1* or *CYP3A5*1/*3* [15].

Statistical Analysis

Statistical analyses were performed with the GraphPad Prism 9.4.1 software (GraphPad Software, Inc). The p-value ≤0.05 was considered statistically significant. A T-test was used to compare demographic variables. The Hardy-Weinberg equilibrium was tested using the Chi-square test. An assessment of the association of genotypes and polymorphic alleles with drug response was carried out using an odds ratio (OR) and with a 95% confidence interval for the odds ratio (95% CI).

Results and Discussion

In the studied population the mean age between males (37.4 ± 8.6 years) and females (33.4 ± 12.8 years) was similar and did not differ significantly (p=0.435). Demographic data are shown in **Table 1**.

Table 1. Demographic and clinical parameters of studied patient groups.

Group	N (%)	Age (y)	Weight (kg)	Height (m)	BMI (kg/m^2)	ARI dose [mg]	Duration of ARI therapy (N/y)	Adverse drug effects

ARI	All	9 (100)	36.56 (±11.66)	70.71 (±27.23)	1.66 (±0.11)	24.84 (±6.54)	2.5 - 30	5/ >1 4/ <1	not observed
	Males	3 (33)							
	Females	6 (67)							
ARI-ADE	All	10 (100)	34.20 (±10.67)	72.29 (±19.64)	1.67 (±0.10)	25.5 (±4.58)	3.75 - 30	4/ >1 6/ <1	Agitation, Anxiety, Somnolence, Hypertension, Akathisia, Increased sleep latency, Weight gain, Reduced motor activity, and Concentration difficulties.
	Males	6 (60)							
	Females	4 (40)							
			p = 0.652	**p = 0.904**	**p = 0.838**	**p = 0.831**			

N - Number
y - year

Genetic profiling was performed on 19 blood samples collected from patients. The distribution of genotypes in the study population was in the Hardy-Weinberg equilibrium ($p \geq 0.05$), except for *CYP2D6* polymorphism. In our analysis, we focused mainly on genes that were involved or probably involved in the metabolism, absorption, and elimination of aripiprazole. Allele and genotype frequencies in both, the ARI and ARI-ADE groups, are shown in **Table 2**.

Table 2. Genotype frequencies of selected polymorphisms.

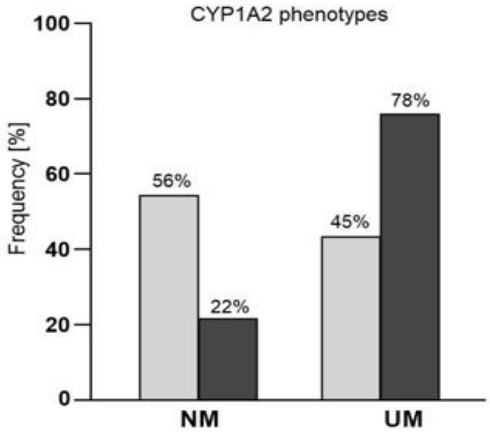
Gene/variants	Genotypes/ Haplotype/ Alleles	Frequency		OR	95%CI
		ARI	ARI-ADE		
	C	0.500	0.650	2.00	0.52-7.69
	T	0.500	0.350	0.50	0.13-1.92
ABCB1 rs1045642	*C/C*	22%	30%		
	C/T	56%	70%		
	T/T	22%	0 %		
	G	0.500	0.688	2.20	0.54-8.96
	A	0.500	0.312	0.45	0.11-1.85
COMT rs4680	*G/G*	22%	37%		
	G/A	56%	62%		
	A/A	22%	0%		
	**1A*	0.333	0.111	0.25	0.04-1.46
	**1F*	0.667	0.889	**4.00**	0.68-23.41
CYP1A2	**1A/*1A*	11%	0%		
	**1A/*1F*	45%	22%		
	**1F/*1F*	45%	78%		
	**1*	0.667	0.900	**4.50**	0.77-26.13
	**6*	0.333	0.100	0.22	0.04-1.29
CYP2B6	**1/*1*	45%	80%		
	**1/*6*	45%	20%		
	**6/*6*	11%	0%		
	WT	0.778	0.850	1.62	0.31-8.48
	Taq1A	0.222	0.150	0.62	0.11-3.23
DRD2 rs1800497	*WT/WT*	56%	70%		
	WT/Taq1A	44%	30%		
	Taq1A/Taq1A	0%	0%		

ARI – patients with aripiprazole monotherapy
ARI-ADE – patients experiencing adverse drug effects and aripiprazole withdrawn

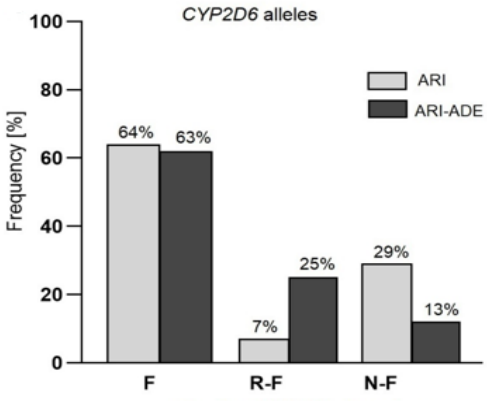
For the polymorphism of the *ABCB1* and *COMT* genes, no homozygous SNP genotypes were observed in the ARI-ADE group (*TT* and *AA*, respectively) **(Table 2)**. Interestingly, in the case of the *CYP1A2* polymorphism, the frequency of the **1F* allele, associated with increased activity, was higher compared to the ARI group (0.889 *vs*.

0.667). The **1A/*1A* genotype (wild-type) was not found in the ARI-ADE group, in turn, homozygous condition (**1F/*1F*) was observed in 78% of patients in this group. Based on the patient's *CYP1A2* genotype, they were classified into two phenotype subgroups: normal or ultra-rapid metabolizer. Only 22% of patients with adverse drug effects belonged to the NM group. Furthermore, we found that the UM phenotype was more common in patients in the ARI-ADE group compared to the ARI group (78% *vs.* 45%, respectively) **(Figure 1a)**. The *CYP1A2*1F* allele may have a predisposing effect on the development of adverse drug effects (OR=4.00, 95% CIs: 0.68-23.41). Comparing the genotype frequency of the *CYP2B6*, we noticed that 80% of patients in the ARI-ADE group were wild-type homozygous (**1/*1*), while in the ARI group, 45% of patients had the same genotype. The odds ratio for the *CYP2B6*1* allele indicated that this allele may increase the chance of developing adverse drug effects (OR=4.50, 95% CIs: 0.77-26.13). The distribution of functional alleles (**1* and **2*) of the *CYP2D6* gene was similar in both the ARI and ARI-ADE groups (64% and 63%, respectively) **(Figure 1b)**. Based on the genotypes we classified patients into two phenotype subgroups: normal and intermediate metabolizer. The NM phenotype was observed more frequently in the ARI-ADE than in the ARI group (75% *vs.* 43%, respectively) **(Figure 1c)**. Regarding the combined CYP3A phenotype all patients in the ARI group and 75% of patients in the ARI-ADE group had IM phenotype **(Figure 1d)**.

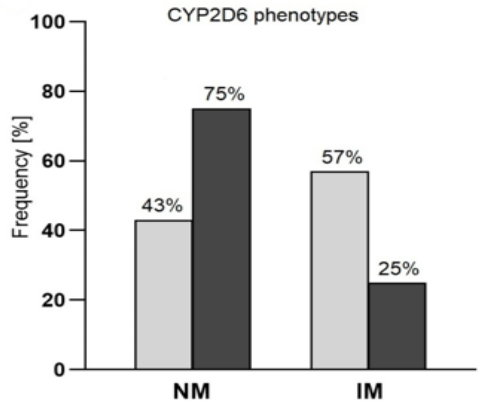
For *DRD2* rs1800497, we found only two genotypes - wild-type homozygotes (*WT/WT*) and heterozygotes (*WT/Taq1A*) in both study groups. In the ARI-ADE group, the *DRD2 WT/WT* genotype was observed as many as 70% of patients, and in the ARI group 56% of patients.



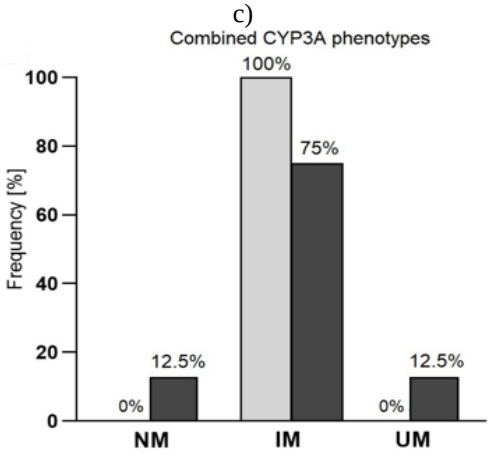
a)



b)



c)



d)

Figure 1. Frequencies of alleles and phenotypes of selected CYPs. ARI – patients with aripiprazole monotherapy, ARI-ADE – patients experiencing adverse drug effects, and aripiprazole withdrawn. NM – normal metabolizers, IM – intermediate metabolizers, UM – ultra-rapid metabolizers. F – functional alleles (sum of **1* and **2*), R–F – reduced-function alleles (sum of **9*, **10*, and **41*), N–F – non-function alleles (sum of **4* and **5*).

In our study, we performed genetic profiling in two groups of patients: the ARI group - patients who received aripiprazole monotherapy and the ARI-ADE group - patients having adverse drug effects after aripiprazole treatment. We

focused mainly on genetic variations in drug-metabolizing and dopamine-degrading enzymes and transporters. The *ABCB1* gene encodes a protein that belongs to the superfamily of ABC protein transporters. This transporter plays a key role in the absorption, distribution, and elimination of drugs [16]. The *ABCB1* rs1045642 (3435C>T) polymorphism influences protein expression. Carriers of the *T* allele are predicted to have low transporter expression and *TT* homozygous had higher T_{max} of ARI and D-ARI [13]. In turn, the enzyme encoded by the C*OMT* gene is involved in the elimination of dopamine in the prefrontal cortex of the human brain. The SNP polymorphism rs4680 (472G>A) causes valine to methionine (Val158Met) substitution that affected protein abundance and enzyme activity [17]. The *AA* genotype is associated with low enzymatic activity resulting in higher levels of dopamine.

Our results showed that there were no differences in the distribution of the *ABCB1* rs1045642 and *COMT* rs4680 genotypes in the two groups of patients, except mutant homozygous (*TT* and *AA*, respectively) that were observed only in the ARI group. Therefore, it seems that these two analyzed polymorphisms were not related to adverse drug effects.

We also assessed genetic variations in the *CYP2D6*, *CYP3A4*, and *CYP3A5* genes that encode enzymes involved in the metabolism of ARI. It is postulated that non-functional alleles are associated with potential adverse effects [18] and extrapyramidal reactions, nausea, or vomiting are more frequently observed in IM and PM patients treated with ARI [5, 19]. Surprisingly, in both our studied groups, the frequency of functional alleles (**1* plus **2*) was similar and accounted for more than 60%, while the frequency of CYP2D6-defective alleles was more than two times higher in the ARI compared to the ARI-ADE group (29% *vs.* 13%, respectively). Moreover, in both groups, we predicted only two phenotypes (NM and IM) based on the patient's genotypes and most of the patients with ADEs were NM. Likewise, combining the *CYP3A4* and *CYP3A5* genotypes, we established that IM was the dominant phenotype in both groups. Thus, our results suggested that normal or intermediate metabolizer status, regarding the *CYP2D6* and *CYP3A* genes, was unlikely to be associated with adverse drug effects.

We also evaluated the frequency of the *CYP1A2* and *CYP2B6* polymorphisms in patients with aripiprazole monotherapy and patients who experienced adverse drug effects. Interestingly, we found differences in the frequency of *CYP1A2* and *CYP2B6* genotypes between the ARI and ARI-ADE groups. The *CYP1A2*1F/*1F* genotype was predominantly observed in the ARI-ADE group (78% vs. 45% in the ARI group), which also corresponded to a higher frequency of the UM phenotype. Regarding the *CYP2B6* genotype, 80% of patients in the ARI-ADE group were homozygous for *CYP2B6*1* (wildtype), so they were classified as normal metabolizers. It is worth emphasizing that 70% of patients in the ARI-ADE group were combined homozygous/homozygous (*CYP1A2*1F/*1F* and *CYP2B6*1/*1*), but there was no observation of this combined genotype in the ARI group. Currently, it is very difficult to find a conclusive explanation for the patient's genotype and susceptibility to adverse drug effects, as aripiprazole is not a substrate for the enzymes CYP1A2 and CYP2B6 (EMEA/H/C/002755/0000). Although recently Koller *et al*. reported that the metabolism of ARI and D-ARI can be influenced by the CYP1A2 enzyme [13]. Surprisingly, the CYP1A2 ultra-rapid metabolizer showed significantly higher ARI AUC and C_{max} as well as D-ARI $T_{1/2}$ compared to normal metabolizers [13]. In addition, during ARI treatment a higher prevalence of insomnia was noticed in NM individuals than in UM individuals [11]. A recent study suggested that patients with higher CYP1A2 activity tended to experience psychic adverse effects less frequently [20]. Our results are inconsistent with previous studies, this discrepancy possibly being due to differences between the study groups and the duration of aripiprazole therapy. In this study, genotyping was performed in psychiatric patients, not in healthy volunteers and our patients were treated with aripiprazole for nearly a year or longer, not just 5 days. ADEs could appear after prolonged exposure to ARI. The brain structure and genetic background in psychiatric patients can differ from healthy individuals.

The main limitation of our study was the low number of patients. In addition, polymorphisms in serotonin receptors and serum/plasma concentration of ARI and D-ARI have not been evaluated. Other factors such as smoking and diet were also not taken into account. Therefore, these preliminary results should be interpreted with caution. Further studies including more participants are necessary to increase the statistical reliability of obtained results.

Conclusion

In the present study, we analyzed genetic variants in psychiatric patients during ARI monotherapy and patients with ADEs related to ARI treatment. Our findings suggest that the distribution of *ABCB1*, *COMT*, *DRD2*, *CYP2D6*, and *CYP3A* polymorphisms were similar in both groups, it seems that they cannot be used as predictors of ADEs. Homozygous status for *CYP1A2*1F* and *CYP2B6*1* was observed more frequently in patients with ADEs than in patients with ARI monotherapy. Additionally, compound genotype *CYP1A2*1F/*1F/ CYP2B6*1/*1* was found exclusively in patients with ADEs. We propose that *CYP1A2* and *CYP2B6* polymorphisms may play a role in the development of ADEs to ARI. However, further studies with a greater number of patients are needed to confirm this association.

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