

Single Nucleotide Polymorphism rs1800497 in Risperidone and Aripiprazole Therapy for Schizophrenia Patients

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ABSTRACT

Schizophrenia is a variable of psychopathologic syndrome involving cognition, emotion, perception, and other behavioral aspects. Therapies on schizophrenia is solely based on history of mental illnesses and mental status. Schizophrenia affecting 1.1 million persons globally in 2017; 70.8% of them happened in 25-55 years old. This study was conducted in mental hospital in Palembang, Indonesia. Blood samples was taken from clinically diagnosed schizophrenia patients (20 patients taking aripiprazole and 60 patients taking risperidone) under therapy. DNA was extracted using Chelex 100 method and digested using Taq1 enzyme. DNA was electrophoresized and visualized. CC allele was found in 10% of patients taking aripiprazole and 11.67% patients taking risperidone. CT allele was found in 70% patients taking aripiprazole and 76.67% patients taking risperidone. TT allele was found in 20% patients taking aripiprazole and 11.67% patients taking risperidone. *ANKKI* Taq1A polymorphism in schizophrenia patients shows different therapeutic response with worse therapeutic response compared to patients with normal allele.

Keywords: rs1800497, Polymorphism, Schizophrenia

I. INTRODUCTION

Schizophrenia is a variable of psychopathologic syndrome involving cognition, emotion, perception, and other behavioral aspects. Clinical manifestation of schizophrenia is variable among

individuals, but usually started before 25 years old of age, has lifelong manifestation, and involves all social classes. Therapies on schizophrenia is solely based on history of mental illnesses and mental status (Sadock & Sadock, 2010). Schizophrenia affecting

1.1 million persons globally in 2017; 70.8% of them happened in 25-55 years old (Metrics, 2019). Globally, schizophrenia prevalence is estimated to be around 0.28% (Charlson *et al.*, 2018).

One of therapeutic agents available in market is aripiprazole. Aripiprazole is a second generation antipsychotics with partial agonism in dopamine D2 receptor (Brunton *et al.*, 2018). Aripiprazole is selectively functional against many isoforms of dopamine D2 receptor (DRD2) (De Bartolomeis *et al.*, 2015; Shapiro *et al.*, 2003). Because of it, aripiprazole is effective against schizophrenia with minimal side effects (De Bartolomeis *et al.*, 2015). Combination between tight conjugation between aripiprazole and DRD2 and partial agonism is postulated to play significant role in better therapeutic profile of aripiprazole compared to other drugs (De Bartolomeis *et al.*, 2015).

Aripiprazole works as selectively functional agent, with variable intrinsic activity and depends on DRD2 signal. DRD2 is a major presynaptic receptor in dopaminergic system. Dopamine is a catecholamine that works in central nervous system and may work as inhibitoric or excitatoric agent, depending on activated dopamine receptor (De Bartolomeis *et al.*, 2015).

Similar to aripiprazole, risperidone is an antagonist of DRD2 in dopaminergic

system (Grant & Fitton, 1994). Risperidone is able to occupy more than 70% of DRD2, creating its antipsychotic activity from dopaminergic antagonism. Risperidone is also able to occupy more than 80% of cortical 5-HT_{2A} receptor, potentially enhancing its antipsychotic properties while reducing extrapyramidal symptoms (Grant & Fitton, 1994; Miyamoto *et al.*, 2005).

Polymorphism of *DRD2* gene is known to play a part in schizophrenia. Single-nucleotide polymorphism that exists also plays in clinical symptoms in patients (Vijayan *et al.*, 2007). Single-nucleotide polymorphism (SNP) in *DRD2* gene plays a role in therapeutic response and side effects of therapy, including therapy with aripiprazole (Ye *et al.*, 2019). *ANKK1* gene in humans exists in chromosome 11.q22-23 and forms a cluster of NTAD (521 kilobase in length) (Mota *et al.*, 2012; Ye *et al.*, 2019). *ANKK1* plays role in modulation of *DRD2* activity (Mota *et al.*, 2012). rs1800497 polymorphism exists on *ANKK1*, a segment 10 kilobase downstream of *DRD2* gene. *ANKK1* gene contains one serine/threonine kinase and becomes a part of protein family that plays a role in signal transduction. rs1800497 polymorphism is located on *ANKK1* exon number 8 (Mota *et al.*, 2012). rs1800497 polymorphism creates a substitution of amino acid in 11th repeat of *ANKK1*, (Glu713Lys

substitution) that changes specificity of DRD2 substrate recognition, that plays a role in dopamine-dependent neuropsychiatric disorders (Neville *et al.*, 2004).

rs1800497 polymorphism in *ANKK1* reduces DRD2 density up to 30%. rs1800497 polymorphism (Taq1A polymorphism) is divided into two alleles, A1 allele (C allele) and A2 allele (T allele) (Klein *et al.*, 2007). rs1800497 polymorphism on *ANKK1* is known to be a risk factor on Chinese schizophrenic population (C. Zhang *et al.*, 2014).

Taq1A polymorphism (rs1800497) on *ANKK1* is known to be involved in therapeutic response of antipsychotics (González-Castro *et al.*, 2016; J. P. Zhang *et al.*, 2015). Schizophrenic patients with A1 allele shows better therapeutic response after therapy with aripiprazole for 4 weeks compared to A2/A2 allele after therapy with aripiprazole (Kwon *et al.*, 2008; Shen *et al.*, 2009).

II. METHODS

This is a descriptive study conducted in a mental hospital in Palembang, Indonesia. All subjects were volunteers aged more than 20 years old diagnosed clinically with schizophrenia and on monotherapy with aripiprazole ($n = 20$) or risperidone ($n = 60$) with no prior history of organic mental disorders or head trauma.

Subjects provided written informed consent after receiving full explanation of study procedures and risks. This research has obtained ethical approval (certificate No. 460/KEPK/RS.ERBA/38454/2020).

DNA was extracted from whole blood using Chelex 100 method. The blood from subjects was extracted in outpatient clinics. *ANKK1* Taq1A polymorphism was detected with PCR-RFLP method in plate thermal cycler (BioRad, USA). The primer used was 5'-GCACGTGCCACCATAACCC-3' (forward) and 5'-TGCAGAGCAGTCAGGCTG-3' (reverse). The PCR profile used was: 5 minutes at 94°C followed by 30 cycles of 30 seconds at 94°C, 40 seconds at 62.8°C, 40 seconds at 72°C, and final annealing of 10 minutes at 72°C. PCR products then digested using Taq1 enzyme. Following digestion, samples were electrophoresized on 4% agarose gel with staining by ethidium bromide. The bands were visualized under UV light and photographed. The results were confirmed by two observers.

III. RESULTS AND DISCUSSION

Our preliminary data suggests increased risk of severe schizophrenia symptoms in patients with rs1800497 polymorphism with higher chance of worse schizophrenia symptoms in subjects taking

risperidone, although our data suggests that the relationship is statistically insignificant. Because of limited subjects participating,

we infer that statistical analysis to prove significance cannot be adequately conducted.

Table I. Genotype and allele frequencies in the aripiprazole ($n = 20$) or risperidone ($n = 60$) groups

SNP	Genotype	DNA band length	Frequency (%)	
			Aripiprazole	Risperidone
ss1800497 (Taq1A)	CC	401, 258 bp	2 (10)	7 (11.67)
	CT	659, 401, 258 bp	14 (70)	46 (76.67)
	TT	659 bp	4 (20)	7 (11.67)
	Allele: C		(45)	(50)
	Allele: T		(55)	(50)

DRD2 is a main presynaptic autoreceptor in dopaminergic system and expressed in all areas of dopaminergic system in brain. DRD3, another member of DRD2-like receptor, also inhibits cAMP production. They are found in postsynaptic areas and have higher density in limbic area, such as in nucleus accumbens. Diversity of dopamine receptors expressed in synaps helps determine response after release of dopamine. Furthermore, this response is not only dependent on synaptic receptor, but also the density of receptors, creating another element of dopaminergic neurotransmission regulation (H. Zhang *et al.*, 2010).

DRD2 gene in humans can be found on chromosome 11q22-23 and contained eight exons with length of 270 kilobase. Some researches show that D2 antagonists block incentive attribution and value motivation, and induced by affective response. In last few years, some

polymorphisms has been identified, such as Taq1A, rs6277, and -141Cins/del. One of the most discussed polymorphism in this gene is Taq1A (rs1800497) polymorphism, a substitution of C allele (A2 allele) to T allele (A1 allele). Some researches has shown the correlation with this polymorphism and major depressive disorder, but the result is inconsistent. There is lack of knowledge between DRD2 polymorphisms and clinical outcomes in patients with major depressive disorders in China (He *et al.*, 2013).

Some researches show that Taq1A polymorphism becomes a risk factor of obesity and Taq1A polymorphism reduces DRD2 density in brain. Decrease of ability for behavioral inhibition with negative consequences and results in activation dysregulation in brain frontal lobe. Taq1A polymorphism is believed to be involved in metabolic syndrome by dopamine dysregulation in dorsolateral part of

prefrontal cortex, orbitofrontal cortex, and cingulate gyrus that results in excessive food administration. Individuals with one or more A1 allele is shown to have 30-40% less DRD2 concentration compared to A2/A2 individuals. Individuals with this polymorphism also has less dopamine receptors in areas of brain that involves in pleasure sensation, thus involved in food administration behavior in obesity (Volkow *et al.*, 2008).

Dopamine is a neurotransmitter synthesized from tyrosine in presynaptic terminal to be released to synaptic cleft. Dopamine is a catecholamine neurotransmitter. Dopamine plays a significant role in movement control, motivation, cognition, satisfaction, and low-level functions, including lactation and sexual pleasure (Seo *et al.*, 2008).

Dopamine is categorized in two groups consisting five subtypes. First group consists of DRD1 and DRD5 that stimulates cAMP formation with G protein stimulation activity. Second group consists of DRD2, DRD3, and DRD4. DRD2 receptors block cAMP formation by inhibiting G protein, with data shown that DRD3 and DRD4 followed similar mechanism of action. Differences between DRD2, DRD3, and DRD4 is in receptor distribution. DRD3 is mainly concentrated in nucleus accumbens and DRD4 is mainly

concentrated in frontal cortex (Neve *et al.*, 2004).

Schizophrenia patients is shown to have increase in dopamine neurotransmitter production. Some researches has identified genes involved in schizophrenia, including DRD2, DRD3, dopamine transporter (DAT), and neuregulin (NRG1) (Sáiz *et al.*, 2010). Dopamine D2 receptor plays role in limbic and caudal area of brain, and has become a target on antipsychotic agents. Changes in transmission and dopamine receptors are hypothesized to be a schizophrenia pathophysiology (Murray *et al.*, 2008). DRD2 is strongly suspected to be involved in schizophrenia (Bulayeva *et al.*, 2007).

Average half-life of elimination of aripiprazole is 75 hours after oral administration; dehydroaripiprazole, its active metabolite, has half-life of 94 hours. Steady state concentration is achieved after 14 days of administration. After oral tablet administration, peak plasma concentration is achieved after 3-5 hours. Oral preparation bioavailability is 87%. Administration simultaneous with foods, including high fat content food, does not affect peak plasma concentration (C_{max}), but increases T_{max} for 3 hours. Volume of distribution in steady-state is high, indicating high extravascular distribution. In therapeutic concentration, aripiprazole and dehydroaripiprazole is 99% bound on

serum protein, mainly albumin. Aripiprazole pharmacokinetics is not affected by age, gender, or body weight. DRD2 saturation is achieved in plasma concentration of 100-150 ng/ml in patients and 100-200 ng/ml in healthy volunteers. Symptoms improvement is observed in serum concentration of 150-300 ng/ml (De Bartolomeis *et al.*, 2015; Katzung, 2018).

Aripiprazole is mainly metabolized by CYP3A4 and CYP2D6 into dehydroaripiprazole and some other metabolites. Dehydroaripiprazole is the metabolized by CYP3A4 and CYP2D6 into other components, and its metabolites are then excreted via urine and feces. Aripiprazole administration concomitant with CYP3A4 or CYP2D6 inhibitors may affect pharmacokinetics profile. Concomitant aripiprazole administration with itraconazole reduces systemic clearance by 30-50% in extensive and intermediate CYP2D6 metabolizers. CYP2D6 polymorphism affects plasma concentration and pharmacokinetics profile of aripiprazole and its active metabolite. In poor metabolizers, increase of 60% is observed compared to normal subjects (De Bartolomeis *et al.*, 2015; Katzung, 2018). Systemic clearance of aripiprazole is reduced significantly in concomitant administration of paroxetine and fluvoxamine. Concomitant administration of aripiprazole and carbamazepine reduces

C_{max} of aripiprazole and dehydroaripiprazole significantly (De Bartolomeis *et al.*, 2015).

Aripiprazole has high affinity for DRD2 and DRD3 in central nervous system; with low affinity for DRD1, DRD4, and DRD5. Aripiprazole has high receptor affinity for 5-HT1A, 5-HT2A, 5-HT2B, and 5-HT7. Aripiprazole has moderate affinity for 5-HT1D and 5-HT2C, and limited for 5-HT1B, 5-HT3, and 5-HT6. Aripiprazole has very low affinity for 5-HT1E dan 5-HT5. Aripiprazole has moderate affinity for alfa1A, alfa1B, alfa2A, and alfa2C, also on H1. Aripiprazole has limited affinity for alfa2B, beta1, beta2, and H3 (De Bartolomeis *et al.*, 2015).

Aripiprazole has very high affinity for DRD2. Aripiprazole is bound to up to 95% of DRD2 in striatum, but does not stimulate DRD2 as well as endogenous ligand, like dopamine. Because of that, intrinsic activity of aripiprazole is not as well as dopamine (De Bartolomeis *et al.*, 2015; Katzung, 2018). Aripiprazole for years is considered to have variable effect on DRD2 and can work as antagonist when the synaptic dopamine concentration increases or work as partial agonist of DRD2 when the dopamine concentration is low. Combination between tight bound with DRD2 and partial agonism is considered to play the role in good

aripiprazole therapeutic profile (De Bartolomeis *et al.*, 2015). Aripiprazole works as selectively functional agent, with variable intrinsic activity depending on DRD2 signal.

Single-nucleotide polymorphism of Taq1A in DRD2 is correlated with schizophrenia susceptibility. Some researches has been conducted to analyze correlation between Taq1A polymorphism and schizophrenia risk, but the result is inconsistent. (Yao *et al.*, 2015). Taq1A polymorphism reduces behavioral inhibition and disruption in activation of brain frontal lobe (González-Castro *et al.*, 2016). Schizophrenia patients with A1 allele shows better therapeutic response after therapy with aripiprazole after 4 weeks compared to A2/A2 allele after therapy with aripiprazole (Kwon *et al.*, 2008; Shen *et al.*, 2009).

IV. CONCLUSION

DRD2 Taq1A polymorphism in schizophrenia patients shows different therapeutic response with worse therapeutic response compared to patients with normal allele.

In the future, the authors suggest to analyze the correlation between different forms of DRD2-related SNPs with other modalities of schizophrenia therapies, including, but not limited to first generation

antipsychotics as mainstay therapies in schizophrenia patients.

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