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Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study

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The aim of the present study was to evaluate the effects of polymorphisms in dopamine D2 receptor (DRD2) and cytochrome P450 (CYP) 2D6 genes on delta EEG power response to aripiprazole in healthy male volunteers. Seventeen volunteers were recruited according to the DRD2 Taq1A genotype, and separated into the following groups: homozygous wild-type (A2/A2, $n=7$), heterozygous (A2/A1, $n=5$) and homozygous variant-type (A1/A1, $n=5$) groups. After enrollment in this study, they were genotyped for CYP2D6. The volunteers received single 10 mg oral doses of aripiprazole, in accordance with an open-label parallel group study design. Plasma levels of aripiprazole and its metabolite were determined and EEGs were obtained simultaneously. The pharmacodynamic parameter was absolute delta power in the Cz channel. The changes of delta power were not different according to DRD2 Taq1A genotypes. As to the CYP2D6 allele, the subjects had the following CYP2D6 genotypes: *10/*10 ($n=4$), *1/*10 ($n=5$), *1/*5 ($n=2$), *1/*1 ($n=3$), *2/*41 ($n=1$), *2/*2 ($n=1$), *2N/*10 ($n=1$). Subjects exhibiting the *1/*5 and *1/*10 genotypes showed a trend toward high area under the plasma aripiprazole concentration-time curve (AUC), which was linearly related to area under the EEG response-time curve (AUEC). Our results demonstrate a need for further evaluation of the CYP2D6 genotypic effect on the pharmacodynamics of aripiprazole.

KEY WORDS — aripiprazole; QEEG; DRD2 Taq1A; CYP2D6

INTRODUCTION

Although clinical response to medication tends to vary broadly in the patients with schizophrenia, this variability currently remains poorly understood. Trials and errors of treatment with antipsychotic drugs are frequently conducted in order to formulate optimal medication regimens.

In recent years, some investigators have reported a relation between genetic variations and drug responses in pharmacotherapy of mental disorders. Genetic variations in dopamine D2 receptor (DRD2), the principal target of antipsychotic drugs, have been studied extensively. Pharmacogenetic research into DRD2 has classically focused on the Taq1A polymorphism, which yields two alleles (the A1 and A2 allele). The minor allele or the A1 allele has been associated with lower DRD2 density values (Noble *et al*., 1991; Thompson *et al*., 1997; Pohjalainen *et al*., 1998; Jonsson *et al*., 1999). The patients with schizophrenia with the A1 allele tended to exhibit superior therapeutic responses to antipsychotic drugs,

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and also manifested more adverse effects (Mihara *et al*., 2000; Suzuki *et al*., 2000; Mihara *et al*., 2001; Schafer *et al*., 2001; Suzuki *et al*., 2001).

Pharmacogenetic research has also underlined the importance of metabolic enzymes. The majority of antipsychotic drugs are metabolized to a significant extent by cytochrome P450 (CYP) enzymes (Dahl, 2002). Depending on the polymorphisms that affect the activities of CYP enzymes, the patients with schizophrenia may exhibit either a toxic accumulation or a rapid elimination of antipsychotic drugs. Among the CYP enzymes, the polymorphic CYP2D6 has been probably the most extensively studied with regard to its impact on the metabolism of antipsychotic drugs (Dahl, 2002). The CYP2D6 polymorphism has been reported to influence the steady-state concentration of several antipsychotic drugs, including perphenazine, zuclopenthixol, risperidone and haloperidol (Dahl *et al*., 1989; von Bahr *et al*., 1991; Llerena *et al*., 1992; Huang *et al*., 1993; Linnet and Wiborg, 1996; Jaanson *et al*., 2002). Poorer metabolizers for CYP2D6 were significantly more prone to drug-induced abnormal movements and tardive dyskinesia during treatment with antipsychotic drugs (Kapitany *et al*., 1998; Ellingrod *et al*., 2000).

Until now, most studies have evaluated the impacts of genetic variation on the pharmacodynamics of antipsychotic drugs, using clinical scales. In spite of the development of sophisticated clinical scales and the achievement of a relatively high degree of inter-rater reliability, objective and quantifiable biological measures and predictors of response to treatment still remain to be established. In recent years, brain-imaging techniques, including quantitative electroencephalography (QEEG), positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI), have bridged this gap to some extent, serving as an intermediate phenotype in pharmacogenetic research. Compared with other brain imaging techniques, QEEG exhibits superior time resolution and is widely used to study the effects of psychotropic drugs, such that the class of the drugs can be inferred from the QEEG profile (Saletu *et al*., 2002).

Aripiprazole has been the focus of increasing clinical attention due to its unique receptor profile as a dopamine partial agonist, and is expected to prove useful in the treatment of schizophrenia with less adverse effects than have been associated with other agents (Grunder *et al*., 2003). Aripiprazole has a high affinity for DRD2, and is eliminated via the actions of CYP2D6 and CYP3A4. This raises the possibility that genetic variations of DRD2 and CYP2D6 might exert some influence on the pharmacodynamics of aripiprazole. However, no pharmacogenetic studies have yet been conducted concerning aripiprazole pharmacodynamics from standpoints of DRD2 and CYP2D6 polymorphisms. Therefore, this study was conducted in order to determine whether or not polymorphisms of DRD2 Taq1A and CYP2D6 might affect the pharmacodynamics of aripiprazole. We used absolute delta power, which exhibited a significant change in the patients with schizophrenia on aripiprazole, as a pharmacodynamic parameter (Canive *et al*., 1998).

METHOD

Subjects

Seventeen right-handed healthy male volunteers participated in this study after each had signed an informed consent. The study protocol of this study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea. The volunteers were from 184 subjects whose genetic information was available prior to the present study, and were recruited according to their DRD2 Taq1A genotypes. They were then divided into the following groups; the homozygous wild type (A2/A2, $n = 7$), heterozygous (A2/A1, $n = 5$), and homozygous variant-type (A1/A1, $n = 5$) groups. After enrollment in this study, all subjects were genotyped for CYP2D6.

The average age ($\pm SD$) of the subjects was 24.4 (± 1.3; age range, 23–28 years) and the average body weight and height of the subjects were 67.7 (± 8.0) kg and 176.1 (± 4.8) cm, respectively. All of the subjects in the study had been completely drug-free for at least 1 month, had not used alcohol and/or caffeine for at least 3 days prior to enrollment in the study, and had no history of medical or psychiatric disease.

Study design

The study was conducted according to an open-label parallel group study design. After fasting overnight for at least 8 h, the subjects received single 10 mg oral doses of aripiprazole, with 240 ml water, at 9 a.m. Considering the pharmacokinetic profile of aripiprazole from previous studies, blood samples for the measurement of aripiprazole and its metabolite (OPC-14857) were obtained just before and 0.5, 1, 2, 4, 6, 9, 12, 24, 48, and 72 h after the administration of aripiprazole. EEG was measured simultaneously with the acquisition of the blood sample. For 24 h, the measurements were conducted in the state of admission and subsequent measurements were taken

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in the outpatient unit of the Clinical Trial Center, Seoul National University Hospital.

DRD2 Taq1A genotyping

Genomic DNA was extracted from the peripheral whole blood of each of the subjects with a Qiagen DNA extraction kit (Qiagen, Hilden, Germany), operated in accordance with the manufacturer's instructions. The presence of the A1 and A2 allele was evaluated via PCR and single base extension, using SNaPshot analysis. The following primers were used for PCR amplification: 5′-gctggccaagttgtctaaat-3′ (forward) and 5′-tggagctgtgaactggact-3′ (reverse). For SNaPshot analysis, the PCR products were purified using exonuclease I and shrimp alkaline phosphatase (USB, Cleveland, Ohio, USA) and then mixed with AmpliTaq DNA polymerase, four fluorescently labeled dideoxynucleotides, each of the primers for single base extension, and the reaction buffer of an ABI PRISM® SNaPshot™ Multiplex Kit (Applied Biosystems), in accordance with the manufacturer's protocols. The primer used for single base extension was 5′-cacagccatcctcaaagtgctggtc-3′ for Taq1A polymorphism. This primer was extended over 25 cycles of 96°C for 10 sec, 50°C for 5 sec, and 60°C for 30 sec. The amplicons were then analyzed using an ABI Prism® 3700 Automated Sequencer (Applied Biosystems). DNA sequences proximal to the polymorphic sites were verified via direct sequencing.

CYP2D6 genotyping

The Genbank accession number used in this study as a reference sequence for the CYP2D6 gene was M33388, but the nucleotide numbering followed the guidelines of the CYP allele Nomenclature Committee homepage, with the A of the translational start codon being defined as +1. CYP2D6 genotyping was conducted for the *2, *5, *10, *17, and *41 alleles, and for the duplication of the CYP2D6 gene. In order to selectively detect the *2, *17, and *41 alleles, we proceeded on the basis of recent reports (Furman *et al*., 2004; Raimundo *et al*., 2004). The DNA near polymorphic sites, −1584C>G, 1023C>T, 2988G>A, was amplified via nested polymerase chain reactions (PCR), followed by automated sequencing analysis. The CYP2D6*10 allele (188C>T) was detected via two-step PCR analysis in accordance with the method developed by Johansson *et al*. (1994). The CYP2D6*5 allele (gene deletion) and gene duplication were detected via long PCR, in accordance with the methods described by Steen *et al*. (1995) and Lundqvist *et al*. (1999), respectively. Alleles containing none of the above described alleles were uniformly classified as CYP2D6*1.

Quantitative EEG measurement

EEG activities were collected using the Neuroscan EEG Synamp and Scan version 4.3 (Neurosoft, USA) in an electrically shielded and soundproofed experimental room in the Clinical Trial Center, Seoul National University Hospital. For the EEG recordings, 15 silver chloride electrodes were positioned according to the international 10–20 system (Fp1, Fp2, F3, F4, Fz, T3, T4, C3, C4, Cz, P3, P4, Pz, O1, O2). All of these electrodes were fixed to the scalp using collodion, and impedance was maintained at below 5 kΩ. These were referred to linked electrodes positioned on the left and right mastoid process. The EEG was recorded continuously using a 0.05–100 Hz analog bandpass filter at sampling rate of 1000 Hz and stored for later analysis. Eyeball movements and blinks were monitored via the electrooculogram.

All subjects sat in a comfortable armchair in a semi-darkened room and remained awake during the EEG recording. The EEG was measured for 3 min per session. The subjects were instructed to remain awake until 12 h elapsed after the administration of aripiprazole, even during the inter-recording periods. They were also constantly monitored so that they did not doze off. The subjects had a normal night's rest 12 h after the administration of aripiprazole, and were instructed to wake up 1 h prior to the recording.

For the subsequent EEG signal processing, artifact-free epochs were selected from each of the recordings. The epoch selection was conducted visually, and EEG segments containing artifacts (muscle activity, ocular artifacts and movement potentials) or showing drowsiness were rejected. The two primary criteria for recognizing drowsiness were (1) the dissolution and fragmentation of occipital alpha rhythm with a shift to the anterior regions and (2) an enhanced frequency variation with a polyrhythmic disintegration of resting EEG into slower and faster components (Bente, 1979; Streitberg *et al*., 1987). The selected individual EEG epochs were then subjected to signal processing, consisting of fast Fourier transformation and spectral analysis. Absolute power in the delta (0.5–4 Hz) frequency band was obtained via spectral analysis.

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Determination of aripiprazole and OPC-14857 plasma levels

Plasma concentrations of aripiprazole and its metabolite OPC-14857 were determined via liquid chromatography-tandem mass spectrometry (LC-MS/MS). In brief, both aripiprazole and OPC-14857, together with their internal standard (OPC-14714), were extracted from the plasma, via liquid–liquid extractions with diethylether. After centrifugation, the organic phase was evaporated to dryness at ambient temperature in a Speed-Vac (Savant, Holbrook, NY). The residue was then reconstituted in 0.2 mL of a mobile phase, and 20 μL of this was analyzed using an API 3000 LC-MS/MS system (Sciex Division of MDS Inc., Toronto, Canada), which had been equipped with an Agilent 1100 series HPLC system (Agilent, Wilmington, DE). The compounds were then chromatographically separated using a Luna CN column (2.0×100 mm, 3 μm; Phenomenex, Torrance, CA), with water and acetonitrile (3/7, v/v) containing 0.1% formic acid mobile phase, at a 0.3 mL/min flow rate. The MS/MS system was operated using an electrospray in positive ionization mode. In order to determine levels of aripiprazole, OPC-14857, and OPC-14714, the following precursor-to-product ion reactions were monitored: m/z 448.1 → 285.2, 446.0 → 285.2, and 458.2 → 295.1, respectively. The coefficient of variation of the intra- and inter-day assays was <10.3%, with accuracy ranging from 97.0 to 108.5%. The lower limit of quantification for both aripiprazole and OPC-14857 was 0.1 ng/ml.

Pharmacokinetic analysis

Pharmacokinetic parameters of aripiprazole and OPC-14857 (C_{max}, t_{max}, AUC, $t_{1/2}$, and CL/F) were calculated for each of the subjects via a non-compartmental method, using WinNonlin® (version 4.0.1, Pharsight Corporation).

Statistical analysis

The PROC MIXED of the SAS system was employed for repeated measures analyses. Mixed effects models were fit with the area under the EEG response-time curve (AUEC) as the dependent variable and with fixed effects for DRD2 Taq1A genotype group (modeled as dummy variable: 1 = A1A1; 2 = A1A2; 3 = A2A2) and hours after the administration of aripiprazole and with random effects for subject. Non-parametric tests were conducted in order to evaluate the group effect on the EEG changes at each time point. Linear regression was employed in the analysis of the relationship between the area under the plasma concentration-time curve (AUC) and AUEC.

RESULTS

Aripiprazole was rapidly absorbed and slowly eliminated. The average time required to achieve peak plasma concentration was 3.2 h, and the average elimination half-life was 56.6 h. The elimination half-life of active moiety (aripiprazole plus OPC-14857) was longer than that of aripiprazole (Table 1). Because the plasma concentrations of OPC-14857 were much lower than those of aripiprazole, we did not include the plasma concentrations of OPC-14857 in pharmacokinetic–pharmacodynamic analysis.

The absolute power of the delta frequency band in the Cz and Fz channels were influenced significantly by the administration of aripiprazole (Cz: df = 10,160, F = 3.743; $p < 0.001$; Fz: df = 10,160, F = 2.673; $p = 0.005$; Figure 1). Although ocular artifacts were extracted via signal processing including visual selection of artifact-free epoch and bandpass filter, we could not completely rule out a possibility that the EEG signal from Fz channel was contaminated by eyeball movement. Therefore we analyzed the EEG signal from Cz channel, and calculated the EEG responses, which were defined via the following equation (1):

$$\text{EEG response(t)} = \frac{\text{absolute delta power at time t} - \text{absolute delta power at baseline}}{\text{absolute delta power at baseline}} \quad (1)$$

The EEG responses in the Cz channel and the mean plasma concentrations of aripiprazole after a single 10 mg oral dose of aripiprazole are provided in Figure 2.

The effects of the DRD2 Taq1 A genotypes on delta EEG power

The AUCs from the baseline to each of the time points did not differ according to the DRD2 Taq1A genotypes (Table 1).

In mixed model analysis, the interaction between DRD2 Taq1A genotype and time after the administration of aripiprazole was not observed. (Table 2).

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Table 1. Summary of the noncompartmental pharmacokinetic parameters of aripiprazole grouped by DRD2 Taq1A genotypes after a single 10 mg oral dose of aripiprazole

	DRD2 Taq1A genotype				
Parameter	A1/A1 ($n=5$)	A1/A2 ($n=5$)	A2/A2 ($n=7$)	p-value*	All ($n=17$) (including OPC-14857)
C_{max} (ng/ml)	47.5 ± 17.4	51.2 ± 13.6	46.4 ± 8.5	0.865	48.1 ± 12.4 (49.8 ± 12.5)
T_{max} (h)	3.1 ± 1.4	3.2 ± 1.7	3.2 ± 1.0	0.773	3.2 ± 1.3 (3.2 ± 1.3)
CL/F (L/h)	3.1 ± 0.7	4.0 ± 0.7	4.6 ± 2.0	0.144	4.0 ± 1.5 (2.8 ± 1.0)
$T_{1/2}$ (h)	65.1 ± 23.1	47.0 ± 14.4	57.3 ± 50.2	0.135	56.6 ± 34.4 (79.2 ± 52.8)
AUC_t (ng · hr/ml)					
0.5 h	3.6 ± 7.1	2.4 ± 2.2	0.4 ± 0.3	0.446	1.9 ± 4.0
1 h	15.0 ± 20.9	12.6 ± 9.5	5.1 ± 2.0	0.353	10.2 ± 12.4
2 h	50.0 ± 44.2	51.0 ± 29.1	32.9 ± 9.3	0.468	43.3 ± 28.5
4 h	132.9 ± 75.7	142.8 ± 59.2	114.7 ± 24.8	0.556	128.3 ± 51.9
6 h	216.9 ± 102.2	230.3 ± 76.8	196.4 ± 29.5	0.556	212.4 ± 68.0
9 h	332.0 ± 138.4	345.5 ± 100.3	305.3 ± 41.1	0.849	325.0 ± 90.9
12 h	438.2 ± 170.5	449.3 ± 126.0	402.0 ± 55.1	0.898	426.5 ± 113.3
24 h	817.5 ± 285.8	807.1 ± 215.1	733.4 ± 113.2	0.919	779.8 ± 196.0
48 h	1422.3 ± 431.1	1342.6 ± 336.4	1238.9 ± 249.8	0.863	1323.3 ± 323.2
72 h	1869.5 ± 510.4	1706.9 ± 399.1	1590.0 ± 408.8	0.443	1705.9 ± 426.5

C_{max}: peak plasma concentration; T_{max}: time to reach peak plasma concentration; CL/F: apparent clearance of drug from plasma; AUC_t: area under the plasma concentration-time curve from 0 to time t; $T_{1/2}$: elimination half-life.
*Kruskal-Wallis test.

The EEG responses at each time point were not affected by the DRD2 Taq1A genotypes, nor were the AUECs from the baseline to each of the time points (Table 3, Figure 3).

The effects of the CYP2D6 genotypes on delta EEG power

The subjects exhibited the following CYP2D6 genotypes: *10/*10 ($n=4$), *1/*10 ($n=5$), *1/*5 ($n=2$), *1/*1 ($n=3$), *2/*41 ($n=1$), *2/*2 ($n=1$), *2N/*10 ($n=1$). The AUCs of aripiprazole in 30 min and 1 h after the administration of aripiprazole differed significantly according to the CYP2D6 genotypes, and we did note a trend toward larger AUC values in subjects with the *1/*5, *1/*10 and *10/*10 genotypes (Table 4).

We could not find any significant linear relationships between AUC and AUEC. However, after the exclusion of two outliers with large residual values,

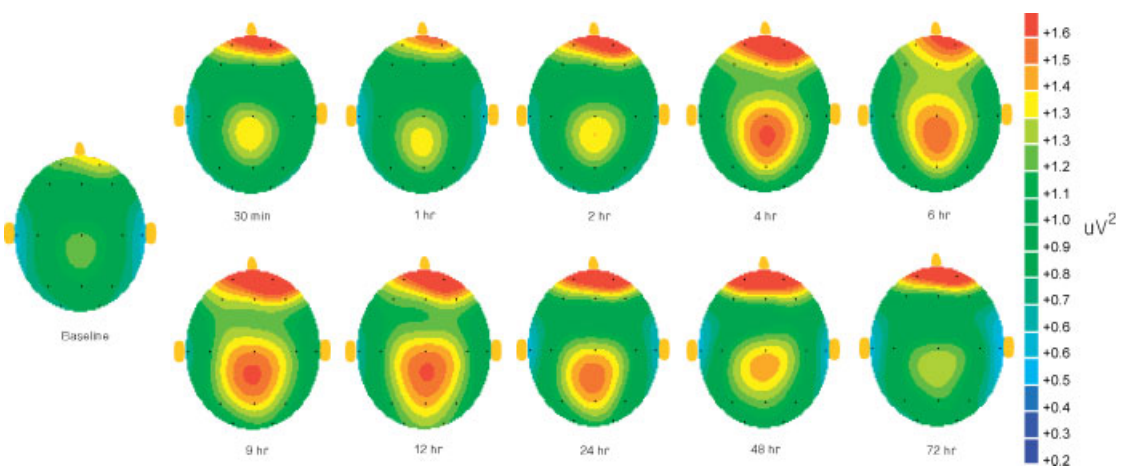

Figure 1. Grand averaged topographic absolute delta power maps after a single oral dose of 10 mg aripiprazole. Two of 17 subjects were not included because their data were available only in Cz and Fz channels. Color bar shows absolute delta power. Images are in bird's view: nose is at the top, left ear is in left side of the subject and right ear is in right side of the subject. Black dots indicate electrode position

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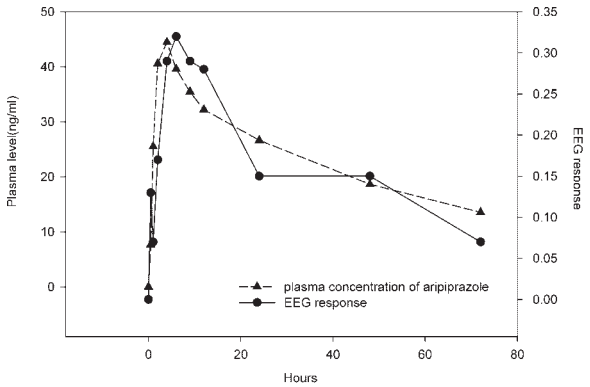

Figure 2. Mean plasma concentrations of aripiprazole and the EEG responses in Cz channel after a single 10 mg oral dose of aripiprazole. EEG response (t) = (absolute delta power at time t − absolute delta power at baseline)/absolute delta power at baseline

which were two standard deviation away from the mean residual value, we were able to observe significant linear relationships between AUC and AUEC in the 2nd hour ($r^2 = 0.372$, $p = 0.016$) and the 6th hour ($r^2 = 0.376$, $p = 0.015$; Figure 4). Subjects with the *1/*5 and *1/*10 genotypes exhibited a trend of larger AUC and AUEC values than did subjects with other CYP2D6 genotypes (Figure 4).

DISCUSSION

Absolute delta power was observed to increase steeply until the 6th hour after the administration of aripiprazole and gradually decreased thereafter (Figure 2). In magnetoencephalographic study, aripiprazole was shown to decrease delta activity in the patients with schizophrenia after 8 weeks of treatment with aripiprazole (Canive *et al*., 1998). Our findings in healthy volunteers differed from the findings of the patient study conducted by Canive *et al*. (1998). This discrepancy might be attributable to differences in the subjects, the duration of aripiprazole administration and the dose of aripiprazole between the two studies. The findings of an *in vitro* study indicated that partial agonists behaved like antagonists under lower receptor density conditions, and like agonists under higher receptor density conditions (McDonald *et al*., 2003). *In vivo* receptor imaging studies reported increased density of striatal DRD2 in the patients with schizophrenia comparing with healthy subjects (Wong *et al*., 1986; Silvestri *et al*., 2000). From this viewpoint, the dopamine partial agonism, manifested

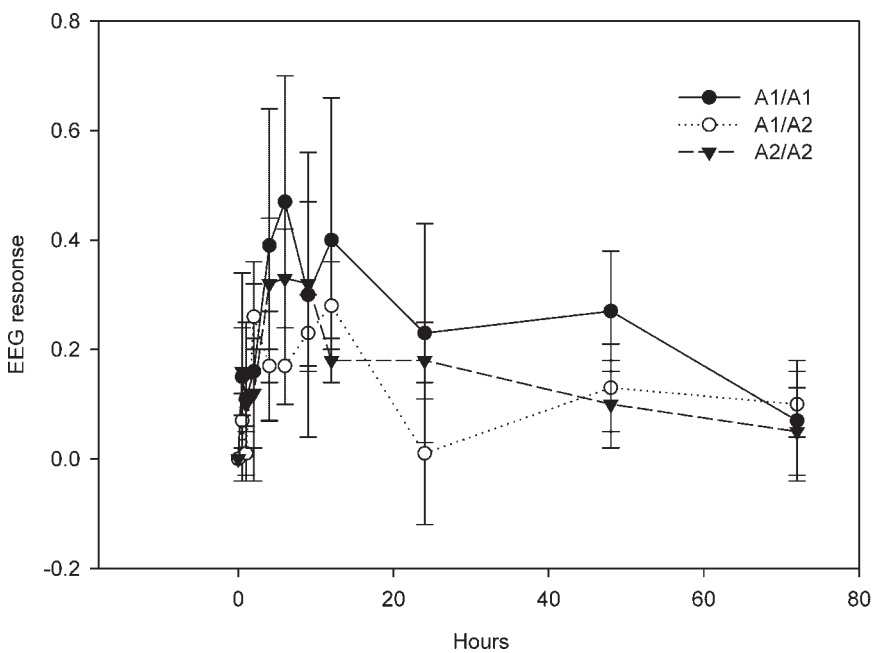

Figure 3. Comparison of the EEG response in Cz channel at each time point among A1/A1 (n = 5), A1/A2 (n = 5) and A2/A2 (n = 7) group. Vertical bars show mean ± SE. No statistical difference was found. EEG response(t) = (absolute delta power at time t − absolute delta power at baseline)/absolute delta power at baseline

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Table 2. Type III test of fixed effects for DRD2 Taq1A genotype*

Source	Numerator (df)	Denominator (df)	F	p-value
Intercept	1.00	28.94	22.90	0.000
Time[†]	10.00	110.20	2.25	0.020
Time * Taq1A[‡]	22.00	84.59	0.76	0.769

[b]*Dependent variable: EEG response.
[†]Hours after the administration of aripiprazole.
[‡]DRD2 Taq1A genotype.

by aripiprazole, might also exert some effects on the discrepancy.

We anticipated that the pharmacodynamics of aripiprazole, which exhibits a high affinity for DRD2, would differ according to the DRD2 Taq1A genotypes. However, we could not observe that the DRD2 Taq1A genotypes had an effect on delta power changes after the administration of aripiprazole. One possible explanation for this result is that the difference of DRD2 density is insufficient to affect delta power change in healthy subjects, in whom an unknown mechanism may be operant, which compensates for the effects generated by the DRD2 Taq1A genotypes. The other explanation is that there might be interaction between the DRD2 genotypes and CYP2D6 genotypes. These explanations are, however, limited, as the sample size was small, and patients with schizophrenia were not included in the present study.

There is a possibility that CYP2D6 genotypes affect the AUC of aripiprazole. The AUCs in 30 min and 1 h after the administration of aripiprazole were significantly different according to the CYP2D6 genotype, and subjects with the *1/*5 genotype exhibited generally higher AUC values after the administration of aripiprazole than did subjects with other genotypes (Table 4, Figure 4). This result is consistent with the findings of previous studies regarding the *5 allele, which features a gene deletion mutation abolishing enzyme expression. Someya *et al*. (1999) reported that subjects with the *5 allele manifested higher plasma concentrations of haloperidol than did subjects with the *1/*1, *1/*10, and *10/*10 genotype. By contrast, Kubo *et al*. (2005) reported that the AUC values for aripiprazole tended to be lower in the *1/*5 group than in the *1/*10 and *10/*10 group. The study by Kubo *et al*. (2005) differs from the present study, in that the AUC from 0 to 336 h after the administration of 3 mg aripiprazole was used to compare pharmacokinetic profiles between CYP2D6 genotypes, and in that the subjects were Japanese. Such differences between the two studies might lead to conflicting results, which requires further pharmacogenetic study.

Because of small sample size, we could not analyze *1/*10 group and *10/*10 group separately. However, Table 4 and Figure 4 showed that subjects with the *1/*10 genotype exhibited a trend toward higher AUC values after the administration of aripiprazole. The *10 allele, which induces reduction of enzyme affinity for the substrate, has been associated with the high plasma levels and AUC values after the administration of several psychoactive drugs, including haloperidol, nortriptyline, paroxetine and aripiprazole (Yoon *et al*., 2000; Dalen *et al*., 2003; Someya *et al*., 2003; Kubo *et al*., 2005). Our findings are in accordance with the previous studies, except that subjects with the *10/*10 genotype exhibited lower AUC values than did the subjects with the *1/*10 genotypes (Figure 4). Although several studies reported that CYP2D6 activity of subjects with the *10/*10 genotype tended to be lower than that of subjects with the *1/*10 genotype (Roh *et al*., 2001; Kim *et al*., 2003), wide variation in the enzyme activity of the subjects with the *10 allele was also

Table 3. EEG response and AUEC by the DRD2 Taq1A genotypes at each time point

Hours	DRD2 Taq1A genotype: A1/A1 ($n=5$)	A1/A2 ($n=5$)	A2/A2 ($n=7$)	p-value*
		EEG response (t)		
0	0	0	0	1
0.5	0.15 ± 0.25	0.21 ± 0.13	0.03 ± 0.13	0.181
1	0.17 ± 0.46	0.16 ± 0.15	0.09 ± 0.16	0.631
2	0.08 ± 0.35	0.26 ± 0.33	0.36 ± 0.28	0.437
4	0.39 ± 0.45	0.38 ± 0.47	0.37 ± 0.47	0.981
6	0.41 ± 0.64	0.40 ± 0.34	0.47 ± 0.45	0.948
9	0.54 ± 0.96	0.47 ± 0.40	0.71 ± 1.32	0.754
12	0.39 ± 0.49	0.27 ± 0.21	0.25 ± 0.23	0.785
24	0.23 ± 0.50	0.23 ± 0.20	0.19 ± 0.33	0.978
48	0.20 ± 0.21	0.21 ± 0.23	0.15 ± 0.20	0.981
72	0.05 ± 0.26	0.16 ± 0.33	0.10 ± 0.17	0.951
		$AUEC_t$		
0.5	0.04 ± 0.06	0.05 ± 0.03	0.01 ± 0.03	0.181
1	0.12 ± 0.21	0.14 ± 0.06	0.04 ± 0.07	0.220
2	0.24 ± 0.60	0.36 ± 0.23	0.26 ± 0.20	0.822
4	0.72 ± 1.30	1.00 ± 0.99	1.00 ± 0.83	0.700
6	1.52 ± 2.33	1.78 ± 1.67	1.84 ± 1.51	0.978
9	2.96 ± 4.60	3.08 ± 2.56	3.62 ± 3.81	0.822
12	4.35 ± 6.69	4.19 ± 3.21	5.06 ± 6.01	0.904
24	8.03 ± 10.71	7.22 ± 4.52	7.66 ± 7.54	0.679
48	13.12 ± 12.62	12.54 ± 8.52	11.74 ± 9.26	0.845
72	16.14 ± 11.55	16.91 ± 13.69	14.81 ± 10.18	0.836

EEG response (t) = (absolute delta power at time t − absolute delta power at baseline)/absolute delta power at baseline.
$AUEC_t$: area under the EEG response-time curve from zero to time t.
*Kruskal-Wallis test.

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Table 4. Summary of the noncompartmental pharmacokinetic parameters of aripiprazole grouped by CYP2D6 genotypes after a single 10 mg oral dose of aripiprazole

Parameter	CYP2D6 genotype			p-value[†]	All ($n = 17$) (including OPC-14857)
	[*]1/[*]5 ($n = 2$)	[*]1/[*]10,[*]10/[*]10 ($n = 9$)	others[*] ($n = 6$)		
C_{max} (ng/ml)	62.9 ± 17.9	47.7 ± 13.5	43.8 ± 5.3	0.302	48.1 ± 12.4 (49.8 ± 12.5)
T_{max} (h)	1.6 ± 0.5	3.3 ± 1.4	3.4 ± 1.0	0.066	3.2 ± 1.3 (3.2 ± 1.3)
CL/F (L/h)	3.5 ± 1.4	3.6 ± 1.4	4.7 ± 1.6	0.424	4.0 ± 1.5 (2.8 ± 1.0)
$T_{1/2}$ (h)	54.7 ± 14.3	64.0 ± 41.8	46.0 ± 26.8	0.161	56.6 ± 34.4 (79.2 ± 52.8)
AUC_t (ng · hr/ml)					
0.5 h	10.4 ± 8.2	1.2 ± 1.5	0.1 ± 0.1	0.018	1.9 ± 4.0
1 h	36.5 ± 21.0	8.3 ± 6.8	4.3 ± 1.6	0.043	10.2 ± 12.4
2 h	97.6 ± 36.6	39.6 ± 23.5	30.8 ± 7.2	0.097	43.3 ± 28.5
4 h	206.8 ± 70.6	123.3 ± 52.2	109.7 ± 18.4	0.127	128.3 ± 51.9
6 h	303.7 ± 115.0	207.2 ± 68.8	189.7 ± 24.6	0.164	212.4 ± 68.0
9 h	433.1 ± 180.2	319.1 ± 89.8	297.8 ± 37.2	0.549	325.0 ± 90.9
12 h	547.1 ± 242.6	420.4 ± 111.3	395.6 ± 49.7	0.646	426.5 ± 113.3
24 h	942.5 ± 472.5	775.1 ± 185.0	732.7 ± 100.7	0.905	779.8 ± 196.0
48 h	1535.9 ± 807.7	1338.2 ± 293.8	1230.3 ± 191.7	0.978	1323.3 ± 323.2
72 h	1957.1 ± 1019.3	1749 ± 385.5	1557.2 ± 285.0	0.722	1705.9 ± 426.5

C_{max}: peak plasma concentration; T_{max}: time to reach peak plasma concentration; CL/F: apparent clearance of drug from plasma; AUC_t: area under the plasma concentration-time curve from 0 to time t; $T_{1/2}$: elimination half-life.
[f*]1/[*]1 ($n = 3$), [*]2/[*]2 ($n = 1$), [*]2N/[*]10 ($n = 1$), [*]2/[*]41 ($n = 1$).
[†]Kruskal-Wallis test.

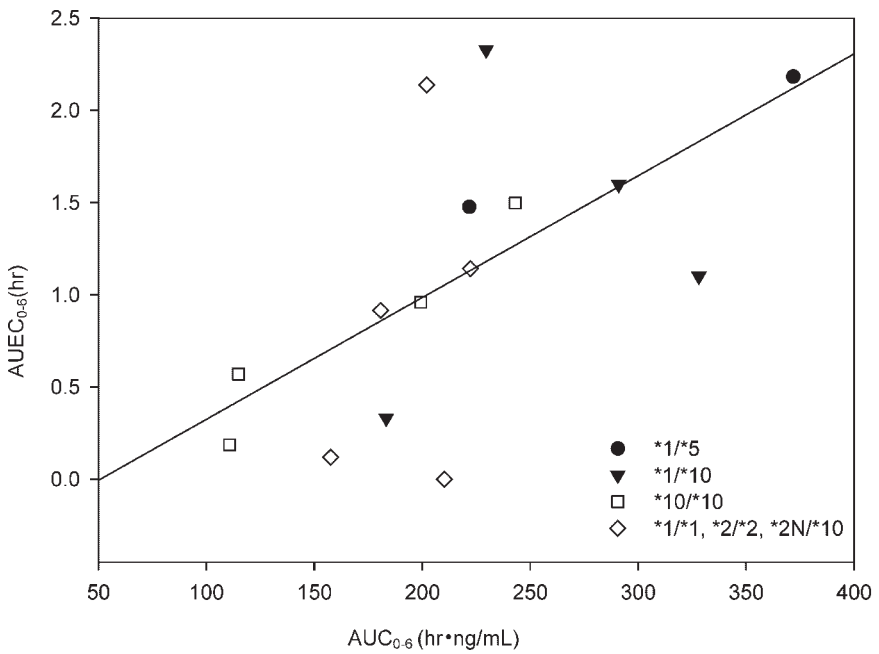

Figure 4. Relationship between $AUC_{0\text{-}6}$ and $AUEC_{0\text{-}6}$. ($r^2 = 0.376$, $p = 0.015$). $AUC_{0\text{-}6}$: area under the plasma aripiprazole concentration-time curve from zero to 6 h; $AUEC_{0\text{-}6}$: area under the EEG response-time curve from zero to 6 h

reported (Yoon *et al*., 2000). Our findings may be under the influence of the wide variation.

CYP2D6 genotypes, which may affect the AUC of aripiprazole, appear to have some influence on its pharmacodynamics. The AUC was related in a linear fashion to the AUEC, and subjects with the [*]1/[*]5 and [*]1/[*]10 genotypes exhibited generally higher AUC and higher AUEC values than subjects with other genotypes. The study by Kubo *et al*. (2005), which reported definite differences in pharmacokinetics of

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aripiprazole between CYP2D6 genotypes, provides supportive evidence for a possibility that the pharmacodynamics of aripiprazole differs according to CYP2D6 genotypes.

This article has attempted to evaluate effects of DRD2 and CYP2D6 genotypes on pharmacodynamics of aripiprazole. Although our preliminary results are not enough to be conclusive, CYP2D6 genotypes appeared to have some influence on the change of delta EEG power. The linear relationship between AUC and AUEC and the trend of different AUC according to CYP2D6 genotypes suggest that the clinical effects of aripiprazole could be influenced by CYP2D6 genotypes and that dose adjustment of aripiprazole could be needed according to CYP2D6 genotypes. Future study, where patients with schizophrenia are well stratified with respect to CYP2D6 genotypes, will be required to ascertain the effect of CYP2D6 genotypes on pharmacodynamics of aripiprazole.

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