The Neurocognitive Effects of Aripiprazole Compared with Risperidone in the Treatment of Schizophrenia

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ABSTRACT

Aripiprazole is a D2 and D3 receptor partial agonist that is unlike other second generation antipsychotics. The effectiveness of aripiprazole with regard to neurocognitive function and its adverse effects is unclear. The present study evaluates the comparative efficacy, effects on neurocognitive function, and adverse effects of aripiprazole and risperidone in the treatment of hospitalized patients with schizophrenia. This double-blind, cross-over study included 23 patients with schizophrenia who were randomly assigned to be treated first with either aripiprazole or risperidone. After eight weeks on one medication, the patients were switched to the other medication for eight weeks. The patient assessment included the Positive and Negative Syndrome Scale (PANSS), neurocognitive assessments, and adverse events including extrapyramidal symptoms, vital signs, electrocardiogram, and clinical laboratory tests. The study findings indicated that psychopathology assessed with the PANSS, extrapyramidal symptoms and other adverse effects did not differ between aripiprazole and risperidone for the subjects remaining in treatment. In the neurocognitive assessments, the score for disinhibition with aripiprazole was significantly lower than with risperidone ($p<0.05$). In addition, serum prolactin levels were significantly lower with aripiprazole ($p<0.001$). The treatment drop-out rate was higher for patients receiving aripiprazole than risperidone. In comparing aripiprazole and risperidone, risperidone is better from the viewpoint of treatment continuation. On the other hand, some adverse effects, such as hyperprolactinemia and disinhibition, are less severe with aripiprazole. Thus, for certain applications, aripiprazole may be a beneficial new treatment option for schizophrenia.

Key words: *Aripiprazole, Neurocognitive functioning, Randomized crossover trial, Schizophrenia*

Schizophrenia is a chronic and severe psychiatric disorder that can deprive afflicted individuals of satisfying participation in social interactions and work. Although schizophrenia is usually defined and treated with reference to psychotic mental processes, cognitive dysfunction is one of the main features of schizophrenia[14]. Research has shown that schizophrenic patients have dysfunctions in working memory, executive function, attention, and verbal fluency[15,37,38,44]. Studies have demonstrated an association between these deficits and poor functional outcomes, including the performance of basic activities of daily living, social skills acquisition, social problem solving, occupational

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Abbreviations: EPS: extrapyramidal symptoms; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. Fourth edition; PANSS: Positive And Negative Syndrome Scale; DIEPSS: Drug Induced Extrapyramidal Symptoms Scale; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; SF-36: 36-Item Short-Form Health Survey; DAI-30: Drug Attitude Inventory; SAI: Schedule for the Assessment of Insight; WAIS-R: Wechsler Adult Intelligence Scale-Revised; FrSBe: Frontal Systems Behavior Scale; TMT: Trail Making Test; VFT: Verbal Fluency Test; WCST: Wisconsin Card Sorting Test; CA: categories achieved; PEM: perseverative errors by Milner's; PEN: perseverative errors by Nelson's; ANOVA: Analysis of Variance; ADHD: Attention Deficit Hyperactivity Disorder

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functioning and community involvement[4,5,19,21,49].

At present, antipsychotic medications are the mainstay of therapy for schizophrenia. Both typical and atypical antipsychotics have efficacy in reducing positive symptoms in some patients, but have limited efficacy regarding negative symptoms and cognitive function. Furthermore, anti-psychotics have side effects including extrapyramidal symptoms (EPS), hyperprolactinemia and weight gain, which limit their use for maintenance treatment[13,28,29,55].

Risperidone was the first atypical antipsychotic drug introduced to Japan, in 1996. Risperidone is a benzisoxazole derivative that has a strong binding affinity for dopamine D2 receptors and serotonin 5-HT2 receptors. Its affinity for serotonin receptors is approximately 200 times greater than that of the conventional antipsychotic haloperidol, while their dopamine antagonistic potencies are comparable. Risperidone demonstrates an antipsychotic efficacy comparable to that of conventional antipsychotics, but shows fewer side effects[48]. It is one of the first line drugs for schizophrenia recommended in the American Psychiatric Association guidelines. However, some patients respond inadequately to risperidone.

The recently developed medication aripiprazole has the unique pharmacological feature of being a partial agonist of dopamine (D2) receptors[22]. In an open label trial, aripiprazole improved positive and negative schizophrenia symptoms as effectively as risperidone and olanzapine[9,40]. In a systematic review, El-Sayeh[11] suggested that aripiprazole reduces schizophrenia symptoms by amounts similar to typical and atypical antipsychotics. Further, aripiprazole produced less akathisia than typical antipsychotics. In addition, patients treated with aripiprazole had lower prolactin levels than those treated with risperidone, olanzapine and typical antipsychotics.

Data is limited about the effects of aripiprazole treatment on cognitive function in schizophrenic patients. One research study using an open-label trial reported that aripiprazole improved cognitive functions such as verbal learning more than olanzapine[31]. This result suggests that aripiprazole may have a different effect on cognitive function compared to other antipsychotics. This difference might be associated with the unique action of aripiprazole as a partial dopamine agonist compared with the full antagonism of other antipsychotics. However, it remains unclear what neurocognitive effects aripiprazole has, and whether there is any difference compared with other antipsychotics such as risperidone.

This study investigates the efficacy of aripiprazole on psychopathology and neurocognitive function, and its adverse effects. The study compares aripiprazole with risperidone in patients with chronic schizophrenia using a double-blinded, randomized crossover study design.

METHODS

1. Participants

The subjects were 23 inpatients (12 men and 11 women) at Kusatsu Hospital whose symptoms corresponded with the diagnostic criteria for schizophrenia according to the DSM-IV[1]. The exclusion criteria included current suicidality, a neurological disorder, an acute or unstable medical condition, a clinically significant laboratory test value, and alcohol or substance dependence within the previous three months. The characteristics of the subjects are presented in Table 1.

The ethics committees of Kusatsu Hospital and Hiroshima University approved the research protocol. The subjects were fully informed about the purpose and procedures of the study, and each subject gave informed consent prior to enrollment.

2. Study Design

The study design was a randomized crossover trial. Subjects were randomly assigned to receive either risperidone or aripiprazole for eight weeks before switching to the other drug for another eight weeks. The dosage of the first drug was adjusted based on the subject's clinical status. For subjects who received the first drug for at least eight weeks, the rater conducted the assessment battery and was blinded to the patient's treatment status.

After the first eight weeks, a psychiatrist switched the first drug to the second drug. At the time of switching, the dose of the first drug was tapered, and finally was discontinued over a period of four weeks. During this tapering period, the second drug was started, and its dosage was increased gradually. The target dose of the second drug was determined from the dose of the first drug (1 mg risperidone = 4 mg aripiprazole). After the completion of the switch, a psychiatrist adjusted dosages of the second drug based on the subject's clinical status. For the subjects who received the second drug for 8 weeks, the same rater conducted the assessment battery again. Concomitant medication with mood stabilizers and anxiolytics was not changed during the study. Whenever needed, benzodiazepines were used to treat agitation and insomnia.

The study design was modified from our previous study[54]. The treatment period of each drug was fixed at eight weeks because this was consistent with the treatment periods of previous studies that investigated the acute effects of newer antipsychotic drugs (4 to 12 weeks), and because our previous study continued one drug for eight weeks.

Table 1. Characteristics of Subjects

Age	38.5 years	SD 14.8
Gender		
Male	12 (52%)	-
Female	11 (48%)	-
IQ (mean on NART)	96.0	SD 11.6
Type of Schizophrenia		
Paranoid	12	-
Disorganized	6	-
Catatonic	4	-
Schizoaffective disorder	1	-
Duration of the Disorder	13.1 years	SD 10.0
Onset of the Disorder	25.9 years	SD 9.5
Antipsychotics Before Enrollment in Study	# Subjects	Average Dosage (mg)
Bromperidol	2	4.5
Haloperidol	1	2.0
Levomepromazine	4	93.7
Olanzapine	4	9.3
Perphenazine	1	12.0
Sulpiride	2	600.0
Nothing	9	-

NART: The National Adult Reading Test

3. Assessment Battery
Pathological symptoms

The schizophrenic symptoms of subjects were assessed by the Positive and Negative Syndrome Scale (PANSS)[30]. Evaluation of extrapyramidal symptoms (EPS) was made using the Drug Induced Extrapyramidal Symptoms Scale (DIEPSS)[25]. Quality of sleep and daytime wakefulness levels were evaluated using the Pittsburgh Sleep Quality Index (PSQI)[7] and the Epworth Sleepiness Scale (ESS)[27]. The PSQI consisted of a questionnaire about sleeping time and interrupted sleep. Higher scores reflect a lower quality of sleep. ESS evaluates wakefulness in daily life. Higher scores indicate lower wakefulness in daily life.

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[26] was used to evaluate general quality of life. This inventory has eight factors and each factor reflects some aspect of quality of life. Higher factor scores indicate higher quality of life. The subjects' attitudes towards their pharmacotherapy were assessed by the Drug Attitude Inventory (DAI-30)[23]. This inventory consists of 30 questions about antipsychotics and pharmacotherapy. Lower scores indicate that subjects have negative attitudes about a medication. In addition, subjects' understandings about their own schizophrenia symptoms were evaluated by the Schedule for the Assessment of Insight (SAI)[10]. The SAI includes questions about the necessity of pharmacotherapy, considerations about the disease, and awareness about schizophrenia symptoms. A lower score reflects less subjective understanding about schizophrenia by the subject.

Some serum constituents (total cholesterol, triglyceride, blood sugar, and prolactin) were measured by blood test. Body weight was also measured.

Neurocognitive function

The neurocognitive function of the subjects was assessed using the following assessment instruments. Counting is a test of short-term memory and working memory, which is part of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[53]. Participants are presented with a series of digits (e.g., '8, 3, 4') and must immediately repeat them back. If they do this successfully, they are given a longer list (e.g., '9, 2, 4, 0'). The score is the number of digits the subject recalled.

The Frontal Systems Behavior Scale (FrSBe)[50] is a 46-item scale assessing behaviors associated with frontal lobe damage including executive dysfunction, apathy and disinhibition. Higher scores indicate higher levels of frontal system problems. We used the self-rated version in this study.

The character discrimination test (Kana-hiroi test)[34] is a test of simple frontal lobe function. Subjects looked at 408 Japanese kana letters randomly listed on paper. Subjects searched for five target letters from a list and circled the target letters during a two minute trial. The dependent variable is the number of letters circled (corrected response).

The Stroop test[45] measures the subject's ability to shift perceptual sets in response to changing demands and to avoid interference from irrelevant stimuli. The subject is asked to read the names of color words (Japanese kanji) drawn in different colored inks (first condition). Next, the subject is asked to name the color of the ink in which the color-word (kanji) is written (second condition). The third condition elicits what is called the Stroop interference effect, where the subject must name the color of the ink which may be at variance with the names of the various color words. The subject, therefore, needs to direct attention towards the color perception and ignore the linguistic stimuli. The dependent variable is the difference between latency for naming all of the colors correctly in this third condition minus that for the second condition.

The Trail Making Test (TMT)[43] has two conditions that combine to assess verbal/spatial perception and psychomotor speed. In Part A, the subject must connect numbers presented on a standard sheet of paper in ascending order (1-2-3). In Part B, the subject must alternate between connecting

Table 2. Scale scores for psychopathological symptoms on risperidone compared to aripiprazole (*n*=18).

	Risperidone		Aripiprazole		
	Mean	SD	Mean	SD	p-value
Dosage(mg)	2.61	1.65	17.50	7.99	-
Conversion of Chlorpromazine	261		438		-
PANSS					
Positive Scale	10.71	3.84	10.94	3.61	0.81
Negative Scale	20.35	7.11	17.00	11.46	0.29
General Scale	29.88	6.84	32.71	8.05	0.14
DIEPSS	1.76	2.75	2.06	3.31	0.21
ESS	3.18	2.72	2.59	2.72	0.46
SF-36					
Bodily Pain (BP)	72.29	29.07	77.29	25.66	0.27
General Health Perception(GH)	47.59	18.43	48.50	24.70	0.75
Mental Health (MH)	56.94	25.16	56.00	24.98	0.87
Physical Functioning (PF)	85.00	16.86	85.88	17.07	0.71
Role-emotional (RE)	58.82	46.44	60.78	44.46	0.85
Social Functioning (SF)	67.65	27.26	70.59	28.96	0.68
Vitality (VT)	64.71	22.53	61.47	31.96	0.54
DAI	13.59	10.41	13.06	9.28	0.83
SAI	11.65	3.67	13.12	5.01	0.10
PSQI	5.29	3.53	6.24	4.74	0.24

numbers and kana letters (for example, 1-あ-2-い-3-う etc.). The amount of time it takes to complete Part A and Part B are the two dependent variables.

Scores on the Verbal Fluency Test (VFT)[12] have been associated with frontal lobe damage, particularly damage to the left frontal lobe. Subjects are given a randomly presented kana letter, and asked to generate a word in response to the presented letter. Each letter is presented for five seconds for one trial. One block consists of six trials. This cycle of six letters was repeated three times. A correct response was defined as a meaningful word beginning with the given letter and not repeated from previous blocks. We calculated number of words generated.

The Wisconsin Card Sorting Test (WCST)[18] assesses executive functions including cognitive flexibility in response to feedback. Performance on this task is known to be impaired in schizophrenia, and is thought to be related to dorsolateral prefrontal cortex dysfunction[16]. Using the computerized WCST software program for administration on a PC, a total of 128 cards are presented. The test requires subjects to sort the cards on the basis of the color, shape, or number of figures. The only feedback provided to the subject is whether each response is correct or incorrect. We calculated the scores of categories achieved (CA), and calculated perseverative errors by Milner's (PEM) and Nelson's

(PEN) methods.

4. Statistical Analysis

Differences between the results on the measures after eight weeks of treatment with risperidone and aripiprazole were evaluated using an Analysis of Variance (ANOVA) for repeated measures. Multiple comparisons were done using the Bonferroni method. A p-value of less than 0.05 was considered statistically significant. To examine order effect, we compared group differences between subjects receiving aripiprazole first and subjects receiving aripiprazole second.

RESULTS

Of the 23 subjects enrolled in our study, 18 completed the entire protocol. Five subjects discontinued due to lack of clinical response or worsening clinical symptoms of schizophrenia during aripiprazole treatment. There were no significant differences in age, gender, IQ, type, duration, onset of schizophrenia, and antipsychotic medication before enrollment, between the subjects who completed the protocol and those who dropped out. However, all patients who dropped out were in the group that received risperidone first. We consider a possible explanation for this drop-out pattern in the discussion section below.

Table 3. Physiological effects of risperidone compared to aripiprazole (*n*=18).

	Risperidone		Aripiprazole		
	Mean	SD	Mean	SD	p-value
Body Weight (kilograms)	65.21	17.36	64.51	16.58	0.42
Serum Constituents					
Blood Sugar (BS)	115.00	46.29	102.11	31.37	0.34
Prolactin (PRL)	51.09	42.62	4.30	5.11	<0.001
Total Cholesterol (T-cho)	188.61	29.34	196.06	38.10	0.17
Triglyceride (TG)	138.06	83.27	123.39	53.21	0.26

Table 4. Cognitive functions on risperidone compared to aripiprazole (*n*=18).

	Risperidone		Aripiprazole		
	Mean	SD	Mean	SD	p-value
Counting (WAIS-R)	11.41	4.18	11.35	3.44	0.93
FrSBe					
Apathy	34.18	11.73	32.29	12.32	0.26
Disinhibition	30.35	10.80	27.24	10.53	0.04
Executive	36.35	10.78	34.41	15.16	0.31
Kana-hiroi Test	39.59	11.56	40.00	11.44	0.68
Stroop Test					
Time(s)	22.05	5.76	22.38	7.72	0.83
Miss	1.14	2.38	0.91	2.18	0.13
TMT(s)					
A	105.76	34.79	105.47	54.18	0.98
B	135.47	68.51	130.53	63.26	0.70
VFT	12.59	2.90	12.41	3.50	0.78
WCST					
CA	4.88	6.16	4.56	5.12	0.61
PEM	4.13	5.52	6.81	11.37	0.20
PEN	6.94	6.19	8.63	11.15	0.32

Pathological and other symptom measures

There was no significant difference found between risperidone and aripiprazole on all the PANSS scales for the 18 subjects who completed the entire protocol. Neither was there any significant difference shown in scores on the DIEPSS, PSQI, ESS, SF36, DAI-30, SAI (see Table 2).

The adverse physiological effect data is shown in Table 3. A significant difference was found between the effect of risperidone and aripiprazole on prolactin (F [1, 16] = 24.50, p<0.001). The mean prolactin level was significantly lower on aripiprazole (4.30 µg/liter). There were no significant differences in changes to other blood serum constituents, nor in changes to body weight.

Comparison of neurocognitive function

Scores for disinhibition assessed on the FrSBe were significantly lower following treatment with aripiprazole, than they were with risperidone. There were no significant differences in other measures of cognitive function between treatment with risperidone and aripiprazole (F [1,16] = 5.27, p<0.05; see Table 4).

DISCUSSION

To our knowledge, this is the first double-blind, randomized cross-over study to evaluate the comparative efficacy, impact on neurocognitive function, and adverse effects of aripiprazole and risperidone in the treatment of hospitalized patients with schizophrenia. Among those who completed the study, aripiprazole and risperidone were equivalent in overall effectiveness in terms of ameliorating positive and negative symptoms of schizophrenia as assessed with the PANSS. They were also equivalent in terms of their effects on other psychopathological symptoms, such as extrapyramidal symptoms (DIEPSS), sleep and wakefulness (PSQI & ESS), general health-related quality of life (SF-36), and attitudes to pharma-cotherapy and understanding of their own disease (SAI). In terms of physiological measures, serum prolactin levels were markedly lower on aripipra-zole than on risperidone treatment.

The present study demonstrated that aripiprazole treatment, compared with risperidone, significantly decreased disinhibition as measured on the Frontal Systems Behavior Scale. Neuropsychological deficits may be a core feature of schizophrenia. They are seen early in the illness, and cannot be entirely attributed to chronicity, antipsychotic medication, or positive symptoms. We used compre-hensive neurocognitive assessment batteries, especially focused on frontal lobe function, and found that aripiprazole had a better treatment effect compared with risperidone with regard to disinhibition in the frontal system.

Impulsiveness is closely related to disinhibition in the frontal system. Individuals who are higher than average in disinhibition are characterized as impulsive, excitable, quick-tempered, and disorderly. The dopaminergic system may play an important role in regulation of impulsive behavior. Suhara and colleagues reported a significant negative correlation between dopamine D2 recep-tor binding in the insular cortex and degree of impulsiveness in healthy young people[47] and decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia[46]. Dopaminergic stimulants such as amphetamine and methylphenidate, improve impulsive behaviors in the treatment of ADHD patients[39].

Aripiprazole, a potent partial agonist of the dopamine D2 receptors[6], has a greater affinity for the D2 receptor than risperidone[20]. The partial agonist property means that, in the presence of dopamine hypoactivity, aripiprazole functions as a dopamine agonist with approximately 30% intrinsic activity at postsynaptic receptors[20]. The precise mechanism of this improvement in disinhibition is not known. However, it is plausible that aripiprazole might have activated dopaminergic

function in the frontal lobe of the patients in this study, which could have resulted in the improvement of disinhibition on the Frontal Systems Behavior Scale.

Relatively little is known regarding the neurocognitive effects of aripiprazole in schizophrenic patients. Kern et al reported the neurocognitive effects of aripiprazole compared with olanzapine on general cognitive functioning, executive functioning, and verbal learning[31]. For general cognitive functioning, both groups improved from baseline. There were no differential treatment effects. For executive functioning, neither group improved significantly from baseline. For verbal learning, the aripiprazole group improved significantly from baseline, and there was a between-group effect favoring aripiprazole over olanzapine. Their results are consistent with our present findings that aripiprazole and risperidone had comparable effects on almost all the neurocognitive assessment batteries, except for disinhibition.

Although the typical dosage of risperidone that our patients received was the commonly rec-ommended dose or lower, their serum prolactin levels were markedly high with risperidone treatment. The switch from risperidone to aripiprazole reduced the elevated serum prolactin levels to a normal reference range. This result is consistent with other reports indicating that aripiprazole lowers prolactin levels and resolves amenorrhea in schizophrenic patients[2, 17]. A recent case report shows successful treatment of ris-peridone-induced hyperprolactinemia by adding aripiprazole[52]. The endocrine processing of prolactin is regulated via dopamine D2 receptors in the pituitary[3]. Dopamine is known to suppress endocrine processes, and the blockade of dopamine receptors by antipsychotic drugs causes the hyperprolactinemia. Aripiprazole, a partial agonist of D2 receptors can therefore inhibit prolactin secretion by functioning as a dopaminergic agonist in the pituitary gland.

Compared with risperidone, aripiprazole has comparable efficacy and favorable adverse effect and tolerability profiles in patients with chronic schizophrenia[8]. However, our study yielded a differential dropout rate for the two drugs, with five patients dropping out from the aripiprazole treatment and none from the risperidone treatment. The switch strategy in our study was a cross-over switching with up-titrating of the new drug and simultaneous tapering off of the initial drug. It has been reported that treatment with aripiprazole leads to an increase in psychotic symptoms in some patients, in the period immediately following switching from risperidone or amisulpiride[33,41,42]. All patients who dropped out from this study received risperidone first and switched to aripiprazole. The most likely ex-

planation for this phenomenon is aripiprazole's partial agonism at dopamine D2 receptors. Aripiprazole acts as a functional antagonist at D2 receptors under hyperdopaminergic conditions but exhibits functional agonist properties under hypodopaminergic conditions[36]. Risperidone shows a high D2 occupancy at daily doses[32]. We postulate that treatment with risperidone created a functional hypodopaminergic state that allowed aripiprazole to act as a dopaminergic agonist, leading to increased psychotic symptoms. When using aripiprazole for the treatment of schizophrenic patients who have been treated with strong D2 antagonists such as risperidone, gradual tapering of the previous antipsychotic drugs after aripiprazole introduction may minimize this phenomenon.

There are serious limitations of our study. First, the number of patients was so small that the statistical power may be inadequate to detect differences between the two treatments. Second, we did not use a placebo control group because of ethical concerns, so we do not know the potential placebo effect in this population. However, the effectiveness of risperidone relative to placebo has been repeatedly reported[24,35,51], so our findings give indirect evidence that aripiprazole is more effective than a placebo. The results of this study could have important implications for the treatment of schizophrenia.

CONCLUSION

Aripiprazole was as effective as risperidone in treating pathological symptoms of schizophrenia in those who completed the study. It showed improvements in disinhibition and hyperprolactinemia in patients with schizophrenia. However, the treatment drop-out rate was higher for patients receiving aripiprazole than risperidone. In comparing aripiprazole and risperidone, risperidone is better from the viewpoint of treatment continuation. On the other hand, some adverse effects, such as hyperprolactinemia and disinhibition, are less severe with aripiprazole. Thus, for certain applications, aripiprazole may be a beneficial new treatment option for schizophrenia.

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