Ther Adv Psychopharmacol
(2012) 2(1) 23–29
DOI: 10.1177/2045125311430536

The influence of switching from oral risperidone to risperidone long-acting injection on the clinical symptoms and cognitive function in schizophrenia

Hidenobu Suzuki and Keishi Gen

Abstract:
Objective: This study was a comparative investigation of the effects on clinical symptoms and cognitive function of switching schizophrenia patients from oral risperidone to risperidone long-acting injection (RLAI) compared with a control group that continued receiving oral risperidone.
Methods: The subjects were 21 patients who had been diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Their clinical symptoms were assessed using the positive and negative syndrome scale (PANSS), and their cognitive function was assessed using the Wisconsin Card Sorting Test: Keio Version (KWCST) to assess executive function, and the St Marianna University School of Medicine's Computerized Memory Test (STM-COMET) to assess memory and concentration.
Results: No significant differences in clinical symptom improvement efficacy were seen between the group that was switched to RLAI and the control group. No significant differences were seen between the two groups in the mean change from baseline in any of the KWCST tests. The mean changes from baseline on the STM-COMET memory scanning test and memory filtering test were significantly greater in the group that switched to RLAI than in the control group. Furthermore, patients with RLAI needed less biperiden, even though they had similar risperidone-equivalent daily dosages as the group with oral risperidone.
Conclusion: The results of this study suggested that switching from oral risperidone to RLAI may affect motor processing function and attention improvement efficacy by allowing the dosage of anti-Parkinson's medication to be reduced.

Keywords: attention, motor processing function, risperidone long-acting injection, schizophrenia

Introduction

In recent years, interest has been increasing in cognitive dysfunction as one of the factors that make it hard for schizophrenia patients to return to society, and atypical antipsychotics, including risperidone, have been considered promising for their efficacy in cognitive dysfunction.

The results of neuropsychological tests have shown that the profile of improvement brought about in cognitive dysfunction by atypical antipsychotics varies depending on the type of antipsychotic [Cuesta *et al*. 2001; Kern *et al*. 2006; Mori *et al*. 2004; Purdon *et al*. 2000; Riedel *et al*. 2007; Suzuki *et al*. 2010].

In 2003, risperidone long-acting injection (RLAI), the first long-acting intramuscular formulation of an atypical antipsychotic, arrived on the market in Germany. RLAI produces less fluctuation in plasma drug concentration and a significantly lower peak in the steady-state plasma concentration than oral risperidone [Eerdekens *et al*. 2004; Kim *et al*. 2009]. This smooth plasma profile has been associated with a decrease in adverse effects, including extrapyramidal symptoms, compared

Correspondence to:
Hidenobu Suzuki, MD, PhD
Department of Psychiatry, Tanzawa Hospital, 557 Horiyamashita, Hadano, Kanagawa, 259-1304, Japan
suzuhide@red.livedoor.com

Keishi Gen, MD, PhD
Department of Psychiatry, Seimo Hospital, Gunma, Japan

with oral risperidone [Moller, 2006; Kim *et al*. 2009]. Furthermore, RLAI, by making it possible to reduce the dose of biperiden more than oral risperidone, is expected to have a beneficial effect on the efficacy of risperidone in improving cognitive function. Against this background, in June 2009, RLAI came on the market in Japan. However, there have not been any reports in Japan clarifying the efficacy of RLAI in cognitive impairment.

In this study, we investigated the effects on efficacy and cognitive function of switching to RLAI in chronic schizophrenia patients receiving oral risperidone.

Methods

Subjects

The subjects were 21 patients who were being treated on an inpatient basis at the psychiatry departments of Tanzawa Hospital and Seimo Hospital and had been diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Chronic schizophrenia patients with cognitive impairment receiving oral risperidone monotherapy were enrolled into this study. Inclusion criteria were: patients with schizophrenia according to the diagnostic criteria of the DSM-IV; patients had been treated with a stable dose of a risperidone monotherapy for at least 3 months. There were no exclusion criteria. In addition, a group of patients (10 subjects) was established as a control group who continued receiving oral risperidone, and whose background characteristics were consistent with those of the patients in the group that were switched to RLAI (11 subjects). The patients had received risperidone monotherapy before they were switched to RLAI. The results were the same as for the control group. There were no other medications besides the study antipsychotic and biperiden.

Furthermore, all the subjects who participated in this study were inpatients whose treatment compliance had been confirmed each time by a nurse, and whose treatment compliance was thus assured. They were required to be symptomatically stable, as judged by the treating psychiatrist, to be able to complete all the neurocognitive measures.

The study was a open-labeled, flexible-dose, naturalistic observational trial of schizophrenia patients undergoing the usual care and who required a change in their medication because of persistent symptoms or troublesome side effects. The oral risperidone group had persistent symptoms or side effects. Patients had high scores in the positive and negative syndrome scale (PANSS), even though they were considered stable. However, these patients could not be considered refractory to antipsychotics.

Subjects were switched to RLAI from their previous therapeutic medications as follows. Subjects were given an initial dose of RLAI 25 mg in addition to their previous therapeutic medications, and received gluteal injections at 2-week intervals, alternating the left and right sides. After 4 weeks, by which point the blood concentration had started to rise, the dosages of the subjects' previous therapeutic medications were reduced so that the subjects received total dosages equivalent to the dosages of their previous therapeutic medications. After 6 weeks, the RLAI dosage was increased as necessary to optimize the dose, and all subjects were receiving RLAI monotherapy. It was therefore possible to investigate the intrinsic effect of cognitive function of RLAI. Following RLAI optimal dose adjustment, wherever possible the dosages of any concomitant medications, including anti-Parkinson's medications, were reduced.

When switching subjects to RLAI, the antipsychotic equivalents calculation table of Inagaki and Inada was used as a guideline for calculating antipsychotic equivalents [Inagaki and Inada, 2010], and the subjects' daily dosages was calculated in terms of risperidone equivalents.

Only patients who had provided voluntarily informed consent in writing to participate in this study upon receiving a full explanation of the purpose and method of the study were enrolled, while patient confidentiality was afforded all due consideration, as were ethical considerations.

Clinical and cognitive assessments

The following clinical and cognitive assessments were performed both at baseline and at 24 weeks by the psychiatrist providing the actual therapy. There were no reliability tests for those who applied the PANSS and cognitive tests. However, assessor training was provided to ensure a certain degree of reliability.

PANSS was used to investigate efficacy [Kay *et al*. 1987]. Cognitive function was assessed using

Table 1. Subject characteristics

Characteristics		Control group	RLAI switching group	p-value
Age (years) (Mean ± S.D.)		45.5 ± 9.8	46.4 ± 12.1	0.56
Gender (M : F)		6 : 4	8 : 3	
Education (years) (Mean ± S.D.)		12.1 ± 2.6	11.7 ± 3.0	0.77
Dulation of illness (years) (Mean ± S.D.)		22.1 ± 8.7	23.2 ± 12.7	0.91
Risperidone equivalents dose (mg/day) (baseline) (Mean ± S.D.)		6.1 ± 1.7	6.0 ± 2.3	0.91
Biperiden equivalents dose (mg/day) (baseline) (Mean ± S.D.)		2.5 ± 1.6	2.4 ± 1.5	0.84
PANSS total score (baseline) (Mean ± S.D.)		85.4 ± 9.3	86.6 ± 12.4	0.80
KWCST				
First stage	CA	1.4 ± 1.7	1.9 ± 1.7	0.50
	PEN	17.0 ± 11.7	19.1 ± 13.8	0.71
	DMS	1.6 ± 1.8	0.8 ± 1.5	0.29
Second stage	CA	1.8 ± 1.6	2.2 ± 0.8	0.49
	PEN	11.1 ± 10.1	13.6 ± 10.1	0.59
	DMS	1.2 ± 1.2	0.9 ± 1.1	0.57
STM-COMET				
IVR		4.9 ± 2.3	5.8 ± 2.4	0.39
DVR		3.3 ± 1.6	3.2 ± 2.0	0.88
DVRG		19.3 ± 8.6	16.8 ± 8.2	0.51
MST		5.4 ± 2.4	6.4 ± 4.8	0.52
MFT		24.0 ± 12.8	29.0 ± 11.4	0.36

RLAI, Risperidone Long-acting injection; PANSS, Positive and Negative Syndrome Scale; KWCST, Wisconsin Card Sorting Test Keio Version; CA, Categories Achieved; PEN, Preservative Errors in Nelson; DMS, Difficulty Maintaining Set; STM-COMET, St. Marianna University School of Medicine's Computerized Memory Test; IVR, Immediate Verbal Recall; DVR, Delayed Verbal Recall; DVRG, Delayed Verbal Recognition; MST, Memory Scanning Test;MFT, Memory Filtering Test

the Wisconsin Card Sorting Test: Keio Version (KWCST) [Kashima, 2002], and St Marianna University School of Medicine's Computerized Memory Test (STM-COMET) [Suzuki *et al.* 2011] as the executive function test and verbal memory function and attention function tests, respectively. The KWCST is the WCST [Heaton *et al.* 1993], which is the most widely used test of frontal lobe function, with several revisions made by Kashima [2002], the most significant of which are the reduction in the number of response cards from Milner's 128 to 48, and the reorganization of the method used to give instructions in two stages. In the instructions given in the first stage, the patient is told that this is a categorization test that uses one of three categorization methods, that is, color, shape, or number, and, in the second stage, the patient is told that the test administrator's category will change occasionally. The STM-COMET comprises five tests [Suzuki *et al.* 2011]: the immediate and delayed verbal recall tests are reflective of the verbal recall function, the delayed verbal recognition is reflective of the verbal recognition function, the memory scanning test involves attention/concentration and information processing ability and is reflective of mental agility, and the memory filtering test is reflective of the ability to maintain one's attention/concentration. Details of the KWCST and STM-COMET are given below. These endpoints were measured at both baseline and 24 weeks after RLAI switching.

Statistical analysis

Direct comparison of the change in each assessment score in the group switched to RLAI and the control group, and comparison of each

Table 2. Mean change from baseline in the risperidone long-acting injection switching group and the control group on clinical symptoms and cognitive function

		Control group				RLAI switching group				p-value
		Baseline		Change frombaseline		Baseline		Change frombaseline		
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Clinical symptoms										
PANSS										
Total		85.4	9.3	−11.5	4.6*	86.6	12.4	−14.3	8.4*	0.37
Positive		17.5	5.4	−2.1	4.5*	18.1	5.9	−3.7	2.9*	0.45
Negative		27.2	3.9	−2.6	2.1*	26.1	3.8	−4.2	3.3*	0.21
General		40.7	3.7	−6.8	2.3*	42.5	7.1	−6.7	3.8*	0.96
Cognitive function										
KWCST										
First stage	CA	1.4	1.7	0.5	1.8	1.9	1.7	1.2	1.3*	0.33
	PEN	17.0	11.7	−4.2	6.1*	19.1	13.8	−10.0	8.3*	0.09
	DMS	1.6	1.8	−0.2	2.9	0.8	1.5	−0.6	1.4	0.66
Second stage	CA	1.8	1.6	1.2	1.0*	2.2	0.8	1.2	0.8*	N.S
	PEN	11.1	10.1	−4.9	7.0	13.6	10.1	−7.7	6.3*	0.37
	DMS	1.2	1.2	−0.3	1.6	0.9	1.1	−0.6	1.0	0.61
STM-COMET										
IVR		4.9	2.3	0.9	2.3	5.8	2.4	1.4	2.1	0.64
DVR		3.3	1.6	0.7	2.2	3.2	2.0	1.4	1.9*	0.46
DVRG		19.3	8.6	0.3	2.8	16.8	8.2	1.5	4.7	0.51
MST		5.4	2.4	6.4	1.9	6.4	4.8	−2.5	4.0*	0.04
MFT		24.0	12.8	0.3	3.2	29.0	11.4	4.5	5.4*	0.04

RLAI, Risperidone Long-Acting Injection; PANSS, Positive and Negative Syndrome Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; KWCST, Wisconsin Card Sorting Test Keio Version;CA, Categories Achieved; PEN, Preservative Errors in Nelson; DMS, Difficulty Maintaining Set; STM-COMET, St. Marianna University School of Medicine's Computerized Memory Test; IVR, Immediate Verbal Recall; DVR, Delayed Verbal Recall; DVRG, Delayed Verbal Recognition; MST, Memory Scanning Test;MFT, Memory Filtering Test
*p<0.05

assessment score before and after switching to RLAI, and continued oral risperidone treatment were analyzed using the Wilcoxon signed-rank test. The associations between cognitive and clinical measures that were significantly improved were analyzed using Pearson's correlations in the group switched to RLAI. The significance level was $p < 0.05$ in all analysis.

Results

No significant differences were seen between the group switched to RLAI and the control group in any of the KWCST or STM-COMET tests, the baseline PANSS total score, the mean daily dosage of the previous treatment drug, the mean duration of illness, the mean number of years of education, or the mean age of the patients (Table 1). None of the patients had withdrawn because of worsening of psychiatric symptoms, adverse reactions, or worsening adherence.

The PANSS total score and the PANSS subscales decreased significantly from baseline in both the group switched to RLAI and the control group, but no significant differences were seen between the two groups (Table 2).

No significant differences were seen between the group switched to RLAI and the control group in the mean changes from baseline in the individual KWCST tests (Table 2). The mean number of categories achieved at the first and second stage of the KWCST was a significant increase from

Table 3. The change over time in the risperidone equivalent dose and the biperiden equivalent dose (mg/day)

	Control group				RLAI switching group				p-value
	Baseline		Change from baseline		Baseline		Change from baseline		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Risperidone equivalent dose (mg/day)	6.1	1.7	−0.6	1.0	6.0	2.3	−1.5	2.0*	0.24
Biperien equivalent dose (mg/day)	2.5	1.6	−0.3	0.7	2.4	1.5	−1.3	1.3*	0.05

RLAI, Risperidone Long-Acting Injection
*p<0.05

baseline (p = 0.02 and 0.01, respectively), and the mean number of preservative errors in Nelson was a significant decrease from baseline in the group switched to RLAI (p = 0.005 in each case). However, the mean change from baseline in the number of categories achieved at level 2 of the KWCST was significantly greater in the control group (p = 0.02). The mean changes from baseline in the memory scanning and memory filtering tests on the STM-COMET were significantly greater in the group switched to RLAI than in the control group (Table 2). The number of items recalled on the STM-COMET delayed verbal recall tests showed a significant increase in the group switched to RLAI ($p < 0.05$). The mean response time (seconds) in the STM-COMET memory scanning test was a significant improvement, and the mean number of items recalled on the STM-COMET memory filtering test was a significant increase in the group switched to RLAI (p = 0.003 and 0.02, respectively). Furthermore, no significant differences were seen in the mean changes from baseline in each of the STM-COMET tests in the control group.

No significant difference was seen between the two groups in the mean change from baseline in the risperidone equivalent dose. The mean change from baseline in the biperiden equivalent dose was significantly lower in the group switched to RLAI than in the control group (Table 3). The mean risperidone equivalent dose and the mean biperiden equivalent dose were a significant decrease from baseline in the group switched to RLAI (p = 0.04 and 0.01, respectively). No significant differences were observed in the control group either in the mean change from baseline in the risperidone equivalent dose or in the mean change from baseline in the biperiden equivalent dose.

Table 4 shows correlations between changes in cognitive function and clinical symptoms before and after switching to RLAI. Most improvements in cognitive function were not correlated with clinical symptoms. Only the improvement in the delayed verbal recall was significantly correlated with changes in the PANSS positive symptoms.

Discussion

No differences were seen in efficacy in the improvement of clinical symptoms between the group switched to RLAI and the control group when inpatients with schizophrenia were given RLAI for 24 weeks, and the efficacy thereof with respect to clinical symptoms was compared with that obtained in the control group, which continued to receive oral risperidone. In addition, although no significant differences were seen between the two groups in the change in risperidone equivalent dose, the risperidone equivalent dose could be reduced in the group switched to RLAI more than in the control group. In overseas clinical studies, switching to RLAI has also been seen to result in lower doses [Schmauss *et al.* 2007]. Furthermore, as described above, considering that it was possible to strive for perfect treatment compliance in this study, switching patients from oral risperidone to RLAI might result in the same clinical efficacy as that achieved with oral risperidone, even if the risperidone equivalent dose is lower than that used with oral risperidone. Moreover, comparison of efficacy in the two groups with respect to cognitive function revealed that superior efficacy in the improvement of motor processing function and attention was obtained in the group switched to RLAI. We therefore infer that the improvement in motor processing function and attention achieved by switching from oral risperidone to RLAI may be

Table 4. Correlations between changes in cognitive and clinical outcomes before and after switching risperidone long-acting injection

	KWCST										
	First stage			Second stage			STM-COMET				
	CA	PEN	DMS	CA	PEN	DMS	IVR	DVR	DVRG	MST	MFT
PANSS											
Total	0.005	0.108	0.001	0.268	0.073	0.252	0.107	0.608*	0.274	0.073	0.143
Positive	0.319	0.123	0.064	0.018	0.171	0.143	0.170	0.650*	0.527	0.255	0.043
Negative	0.237	0.048	0.039	0.265	0.181	0.210	0.106	0.369	0.104	0.214	0.206
General	0.033	0.185	0.018	0.385	0.139	0.274	0.014	0.529	0.111	0.176	0.107

PANSS, Positive and Negative Syndrome Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; KWCST, Wisconsin Card Sorting Test Keio Version;CA, Categories Achieved; PEN, Preservative Errors in Nelson; DMS, Difficulty Maintaining Set; STM-COMET, St. Marianna University School of Medicine's Computerized Memory Test; IVR, Immediate Verbal Recall;DVR, Delayed Verbal Recall; DVRG, Delayed Verbal Recognition; MST, Memory Scanning Test; MFT, Memory Filtering Test
*p<0.05

due to the pharmacokinetic profile of RLAI, that is, a lower steady-state plasma concentration peak. The smooth pharmacokinetic profile of RLAI may result in less of the excessive sedation that occurs with antipsychotics than is seen with oral risperidone (Moller, 2006). However, since no blood concentration measurements were taken and excessive sedation was not systematically evaluated in patients receiving RLAI in this study, this is nothing more than an informed guess. The results of this study reveal that the significant reduction in the biperiden equivalent dose in the group switched to RLAI compared with the control group may be one of the reasons a difference was seen between the two groups in efficacy with respect to cognitive function.

In clinical studies overseas, risperidone has been reported to improve perception, attentiveness, motor processing function, executive function, language learning, memory, and verbal fluency [Meltzer and McGurk, 1999]. In an overseas clinical study, on the other hand, Kim and colleagues investigated the effect of RLAI on cognitive function in a 26-week, open-label study. RLAI was found to improve significantly attention, visuomotor speed, verbal learning and memory, and executive function [Kim *et al*. 2009].

The aforementioned results suggest that switching from oral risperidone to RLAI may, by alleviating drug-induced sedation and allowing the dose of anti-Parkinson's medication to be reduced, affect the efficacy in improvement of motor processing function and attention. These results are consistent with the results of previous research. However, because compliance was good, this suggested that it would be possible to perform similar comparisons of the effects of RLAI and oral risperidone on the efficacy and cognitive function. In this study, changes in most cognitive functions were not correlated with changes in clinical symptoms. Also, since patient treatment compliance prior to RLAI switching had been assured, this suggested that it would be possible to assess to a certain extent the efficacy of RLAI switching in cognitive impairment. Therefore, the majority of cognitive improvements in this study could be independent of those in clinical symptoms.

Limitations

This study had a relatively small sample size, and was a short-term study (24 weeks), and also was an open-label, not a double-blind, study, so the possibility that bias was introduced to the results cannot be ruled out, and there are consequently limits to the conclusions that can be drawn from this study. The greatest problem in this study is that it is impossible to rule out the possibility that the concomitant use of anti-Parkinson's medication may have masked changes in cognitive function that should have been observed. A double-blind, randomized, controlled study with subjects who are not taking concomitant anti-Parkinson's medication potentially affecting cognitive function may be necessary in the future in order to clarify the effect that RLAI has on cognitive dysfunction.

Conclusion

This study was a comparative investigation of the effects on clinical symptoms and cognitive function of switching schizophrenia patients from oral risperidone to RLAI compared with a control group that continued to receive oral risperidone. Patients with RLAI needed less biperiden, even though they had similar risperidone-equivalent daily dosages as the group with oral risperidone. The results of this study suggested that switching from oral risperidone to RLAI may affect motor processing function and attention improvement efficacy by allowing the dosage of anti-Parkinson's medication to be reduced.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Cuesta, M.J., Peralta, V. and Zarzuela, A. (2001) Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. *Schizophr Res* 48: 17-28.

Eerdekens, M., Van Hove, I., Remmerie, B. and Mannaert, E. (2004) Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. *Schizophr Res* 70: 91-100.

Heaton, R.K., Chelune, G.L., Talley, J.L., Kay, G.G. and Curtiss, G. (1993) *Wisconsin Card Sorting Test Manual: revised and expanded*. Odessa, FL: Psychological Assessment Resources.

Inagaki, A. and Inada, T. (2010) Dose equivalence of psychotropic drugs. Part XXII: dose equivalence of depot antipsychotics III: risperidone long-acting injection. *Jpn J Clin Psychopharmacol* 13: 1349-1353 (in Japanese).

Kashima, H. (2002) Tests for executive function. *Jpn Psychiatry Diagnostic* 13: 205-212 (in Japanese).

Kay, S.R., Fiszbein, A. and Opler, L.A. (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13: 261-276.

Kern, R.S., Green, M.F., Cornblatt, B.A. Owen, J.R., McQuade, R.D., Carson, W.H. *et al.* (2006) The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology (Berl)* 187: 312-320.

Kim, S.W., Shin, I.S., Kim, J.M., Lee, Y.H., Yang, S.J. and Yoon, J.S. (2009) Effects of switching to long-acting injectable risperidone from oral atypical antipsychotics on cognitive function in patients with schizophrenia. *Hum Psychopharmacol* 24: 565-573.

Meltzer, H.Y. and McGurk, S.R. (1999) The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 25: 233-255.

Moller, H.J. (2006) Long-acting risperidone: focus on safety. *Clin Ther* 28: 633-651.

Mori, K., Nagano, M., Yamashita, H., Morinobu, S. and Yamawaki, S. (2004) Effect of switching to atypical antipsychotics on memory in patients with chronic schizophrenia. *Progr Neuropsychopharmacol Biol Psychiatry* 28: 659-665.

Purdon, S.E., Jones, B.D.W., Stip, E., Labelle, D., Addington, S.R., David, A. *et al.* (2000) Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. *Arch Gen Psychiatry* 57: 249-258.

Riedel, M., Muller, N., Spellmann, I., Engel, R.R., Musil, R., Valdevit, R. *et al.* (2007) Efficacy of olanzapine *versus* quetiapine on cognitive dysfunctions in patients with an active episode of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 257: 402-412.

Schmauss, M., Sacchetti, E., Kahn, J.P. and Rossella, M. (2007) Efficacy and safety of risperidone long-acting injectable in stable psychotic patients previously treated with oral risperidone. *Int Clin Psychopharmacol* 22: 85-92.

Suzuki, H., Gen, K. and Inoue, Y. (2010) An unblended comparison of clinical and cognitive effects of switching from first-generation antipsychotics to aripiprazole, perospirone or olanzapine in patients with chronic schizophrenia. *Progr Neuropsychopharmacol Biol Psychiatry* 35: 161-168.