A Cross-Sectional Study of Plasma Risperidone Levels With Risperidone Long-Acting Injectable: Implications for Dopamine D_2 Receptor Occupancy During Maintenance Treatment in Schizophrenia

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ABSTRACT

Objective: While 65%–80% occupancy of dopamine D_2 receptors with antipsychotics has been proposed to achieve optimal therapeutic response during acute treatment of schizophrenia, it remains unclear as to whether it is also necessary to maintain D_2 receptor occupancy within this "safe" window for ongoing maintenance treatment. The data are especially scarce for long-acting antipsychotic formulations.

Method: Clinically stable patients with schizophrenia (*DSM-IV*) receiving a stable dose of risperidone long-acting injectable (LAI) as antipsychotic monotherapy for at least 3 months and free of any psychiatric hospitalization over the past 6 months were included. Dopamine D_2 receptor occupancy levels at trough were estimated from plasma concentrations of risperidone plus 9-hydroxyrisperidone immediately before the intramuscular injection of risperidone LAI, using a 1-site binding model derived from our previous positron emission tomography data. This study was conducted from October to December 2011.

Results: 36 patients were included in this study (mean ± SD age, 49.3 ± 14.0 years; mean ± SD dose and interval of injections, 38.2 ± 11.6 mg and 16.5 ± 14.0 days, respectively). Mean ± SD D_2 receptor occupancy was 62.1% ± 15.4%; 52.8% of the subjects (n = 19) did not demonstrate an occupancy of ≥ 65%. On the other hand, 13.9% (n = 5) showed a D_2 occupancy as high as over 80% at the estimated trough.

Conclusions: More than half of patients taking risperidone LAI maintained clinical stability without achieving continuous blockade of dopamine D_2 receptors ≥ 65% in real-world clinical settings. Results suggest that sustained dopamine D_2 receptor occupancy levels of ≥ 65% may not be necessary for maintenance treatment with risperidone LAI in schizophrenia.

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Schizophrenia is, in general, a chronic and debilitating psychiatric illness requiring long-term antipsychotic treatment.[1,2] Because antipsychotic drugs not only improve psychotic symptoms but also prevent relapse,[3] regular dosing of antipsychotics is considered critical to any successful maintenance treatment strategy. Long-acting depot antipsychotic medications ensure reliable drug delivery in patients for whom adherence with oral medications is a concern,[4] resulting in a decreased risk of relapse compared with oral agents.[5,6] Among them, risperidone long-acting injectable (LAI) is the first atypical antipsychotic drug available in depot formulation. Previous clinical studies have shown that risperidone LAI is effective for both short-term[7] and long-term[8,9] treatment of schizophrenia.

Antipsychotic efficacy is linked to dopamine D_2 receptor blockade, a feature shared in common by all currently available antipsychotics.[10] Previous brain imaging studies have consistently shown the presence of a therapeutic window of 65%–80% occupancy in striatal dopamine D_2 receptors that is associated with optimal chance of therapeutic efficacy during acute treatment while minimizing risks of extrapyramidal symptoms (EPS) and cognitive impairment.[11] That said, it still remains unclear as to whether it is also necessary to maintain D_2 receptor occupancy within this range for ongoing maintenance treatment. This issue is highly relevant to clinical practice because prolonged antipsychotic therapy exposes patients to numerous dose-dependent side effects such as EPS, negative subjective well-being, cardiac sudden death, and cognitive impairment.[11–14] It therefore would be ideal if exposure to antipsychotic drugs could be minimized during maintenance treatment. Of note, positron emission tomography (PET) data suggest that sustained D_2 receptor blockade ≥ 65% may not be necessary to maintain clinical response. In one PET study,[15] 7 subjects with schizophrenia who were receiving risperidone LAI were followed up for a 1-year interval, and although more than 50% of subjects showed < 65% D_2 receptor occupancy at trough on PET examinations, none relapsed over the follow-up period. To our knowledge, there have been only 2 PET studies that measured dopamine D_2 receptor occupancy with risperidone LAI,[15,16] and the samples sizes were only 9 and 7, respectively. More data regarding dopamine D_2 receptor occupancy and risperidone LAI are clearly warranted to better understand occupancy-response relationship.

However, the clear limitation to accessing PET due to its high cost and lack of wide availability represents a real and significant

Clinical Points

- More than half of clinically stable schizophrenia patients taking risperidone long-acting injectable (LAI) did not show continuous blockade of dopamine D_2 receptors > 65%.
- Sustained dopamine D_2 receptor occupancy levels of ≥ 65% may not be necessary for maintenance treatment with risperidone LAI in schizophrenia.
- Optimizing the dosing and/or dosing intervals of antipsychotics could maximize effectiveness while reducing risk of side effects.

challenge to addressing the occupancy-response relationship with risperidone LAI in a large sample. Clinical translation of drug occupancy studies, therefore, is only possible if widely available laboratory plasma antipsychotic assays can be reliably used for bedside estimation of central drug binding. This said, recent data have demonstrated that dopamine D_2 receptor occupancy of antipsychotic drugs, including risperidone, can be estimated with a high degree of precision from plasma drug concentrations, using a 1-site binding model.[17] We therefore conducted a cross-sectional study to evaluate dopamine D_2 receptor occupancy levels in clinically stable patients with schizophrenia who were maintained on risperidone LAI treatment for at least 3 months and were free of psychiatric hospitalization for at least 6 months. In this study, dopamine D_2 receptor occupancy at trough with risperidone LAI was estimated from plasma concentrations of risperidone plus 9-hydroxyrisperidone based on our previously published phemakokinetic-pharmacodynamic data for risperidone and 9-hydroxyrisperidone.[15,16]

METHOD

Participants and Settings

A consecutive series of outpatients who visited one of the participating sites were invited to participate in the study if they met the following inclusion criteria: (1) *DSM-IV* diagnosis of schizophrenia[18]; (2) treatment with a stable dose of risperidone LAI over the previous 3 months; (3) no hospitalization for psychiatric conditions over the previous 6 months; and (4) the capability to provide voluntary, informed consent. Patients were excluded if they were receiving any other depot or oral antipsychotic drug, with the exception of oral antipsychotics used at bedtime in doses ≤ 100 mg chlorpromazine equivalents for the purpose of sedation, doses that are considered subtherapeutic if used as monotherapy and often used clinically to manage other associated symptoms including insomnia.[19] This study was conducted at Asakadai Mental Clinic, Saitama, Japan; Inokashira Hospital, Tokyo, Japan; Ohizumi Mental Clinic, Tokyo, Japan; Ohizumi Hospital, Tokyo, Japan; Toyoko-Keiai Hospital, Kanagawa, Japan; Komagino Hospital, Tokyo, Japan; and Minamihannou Hospital, Saitama, Japan, from October to December 2011. The study was approved by the institutional review board at each of the participating sites, and, prior to study entry, participants provided voluntary, written informed consent after receiving detailed information about the protocol.

Study Description

One plasma sample was taken for the measurement of risperidone plus 9-hydroxyrisperidone (active moiety) immediately before the intramuscular injection of risperidone LAI, which represented trough concentrations. Plasma concentrations of risperidone and 9-hydroxyrisperidone were assayed in heparinized plasma using LC/MS/MS (liquid chromatography with tandem mass spectrometry detection) with a limit of quantitation of 2 nmol/L (0.82 ng/mL) and 5 nmol/L (2.13 ng/mL), respectively. The following information was also collected: concomitant medications, interval between the last injection of risperidone LAI and plasma sampling, age, sex, race, and duration of illness. Participants were evaluated with the following assessments: the Brief Psychiatric Rating Scale (BPRS),[20] the Simpson-Angus Scale (SAS),[21] the Barnes Akathisia Scale (BAS),[22] and the Abnormal Involuntary Movement Scale (AIMS).[23]

Dopamine D_2 Receptor Occupancy

Dopamine D_2 receptor occupancy levels were estimated by incorporating the estimated plasma concentration of risperidone plus 9-hydroxyrisperidone into the following 1-site binding model: occupancy (%) = $100 \times$ [plasma concentration/(plasma concentration + ED_{50})], where ED_{50} is the estimated plasma concentration of the antipsychotic drug associated with 50% of receptor occupancy, which was obtained from a total of 15 patients who participated in our previous 2 PET studies.[15,16] Because the study by Remington et al[16] included 2 PET scans per patient, only data from the first scan were included in the analysis. Thus, ED_{50} was calculated to be 10.5 ng/mL (95% confidence interval, 7.6–13.4; $R^2_{15} = 0.71$). For patients receiving concomitant antipsychotic drugs, dopamine D_2 receptor occupancy levels derived from risperidone LAI plus those concomitant drugs were also estimated. Those concomitant doses were converted to risperidone LAI equivalents,[19] and then added to the original risperidone LAI doses. Plasma concentrations of risperidone plus 9-hydroxyrisperidone were multiplied by the new risperidone dose/the original risperidone LAI dose in light of a linear relationship between risperidone LAI dose and plasma drug concentration.[24] Corresponding dopamine D_2 receptor occupancy was subsequently calculated.

Data Analysis

Statistical analyses were carried out using SPSS Version 18.0 (SPSS Inc, Chicago, Illinois) and PRISM Version 5 (GraphPad Software Inc, San Diego, California). Spearman rank correlation analysis was used to examine the relationship between estimated dopamine D_2 receptor occupancy levels and clinical assessment scores. A P value of < .05 was considered statistically significant (2-tailed).

Table 1. Demographic and Clinical Characteristics of 36 Patients With Schizophrenia

Characteristic	Value
Age, mean ± SD (range), y	49.3 ± 14.0 (21–74)
Sex, male, n (%)	15 (41.7)
Ethnicity, Japanese, n (%)	36 (100)
Duration of illness, mean ± SD (range), y	22.6 ± 12.6 (2–48)
Dose of risperidone LAI, mean ± SD (range), mg	38.2 ± 11.6 (25–50)
Interval of injections, mean ± SD (range), d	16.5 ± 14.0 (13–28)
BPRS total score, mean ± SD (range)	35.4 ± 13.1 (18–64)
SAS total score, mean ± SD (range)	2.2 ± 2.7 (0–10)
AIMS total score, mean ± SD (range)	2.9 ± 3.0 (0–12)
BAS total score, mean ± SD (range)	0.4 ± 1.1 (0–5)

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, LAI = long-acting injectable, SAS = Simpson-Angus Scale.

RESULTS

Patient Characteristics

Recruitment took place from October to December 2011. During the recruitment phase, a systematic screening of all consecutive outpatients who visited one of the participating sites in Japan was performed. Thirty-six patients who fulfilled the inclusion/exclusion criteria were identified and approached for participation in this study; of these, 36 patients (100%) agreed to participate and completed all study procedures. Demographic and clinical characteristics of the patients are summarized in Table 1. Sixteen (44.4%), 6 (16.7%), and 14 (38.9%) of the patients received 50 mg, 37.5 mg, and 25 mg of risperidone LAI, respectively; the most frequent interval of injections was 2 weeks (n = 25, 69.4%). Eleven patients (30.6%) received a concomitant antipsychotic medication of ≤ 100 mg chlorpromazine equivalent dose at bedtime; levomepromazine was the most frequent drug (n = 6; dose: 25, 25, 25, 25, 50, and 100 mg/d, respectively), followed by chlorpromazine (n = 4; dose: 25, 25, 37.5, and 75 mg/d, respectively), sulpiride (n = 1, dose, 100 mg/d), and quetiapine (n = 1, dose: 25 mg/d). Of these, 1 patient concomitantly received levomepromazine 25 mg/d and sulpiride 100 mg/d. The mean ± SD chlorpromazine equivalent dose was 45.5 ± 26.4 mg/d.

Estimated Dopamine D_2 Receptor Occupancy

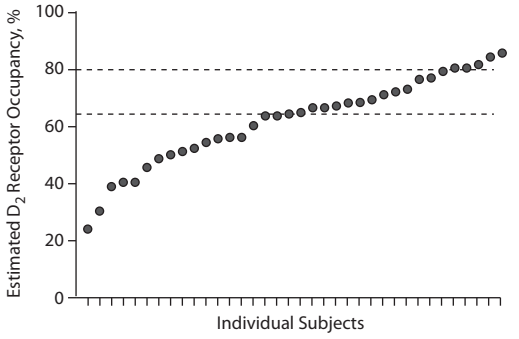
Mean ± SD (range) concentration of risperidone plus 9-hydroxyrisperdione at trough was 22.5 ± 15.0 (64.6–3.3) ng/mL. Estimated dopamine D_2 receptor occupancy levels that correspond to those trough plasma concentrations are shown in Table 2 and Figure 1; mean ± SD D_2 receptor occupancy was 62.1% ± 15.4%. Nineteen of the patients (52.8%) did not demonstrate occupancy ≥ 65%; on the other hand, 13.9% (n = 5) showed a D_2 occupancy as high as > 80%. No correlations were observed between estimated D_2 receptor occupancy levels and the BPRS, SAS, AIMS, or BAS total scores. Additionally, when the effects of concomitant antipsychotics on dopamine D_2 receptor occupancy were taken into consideration, half of the patients (n = 18) showed < 65% occupancy.

Table 2. Plasma Concentrations, Estimated Dopamine D_2 Receptor Occupancy, and Clinical Assessment Scores in 36 Patients Receiving Risperidone LAI

	Risperidone Active Moiety		Clinical Assessments, Total Score			
Patient No.	Plasma Concentration, ng/mL	D_2 Occupancy, %	BPRS	SAS	BAS	AIMS
1[a]	3.3	24.2[b]	33	0	0	0
2	4.6	30.5[b]	20	0	0	1
3[a]	6.7	39.1[b]	41	5	0	2
4	7.2	40.6[b]	33	0	0	7
5	7.2	40.6[b]	54	3	0	0
6	8.8	45.6[b]	18	0	0	0
7[a]	10.0	48.9[b]	18	0	0	0
8	10.8	50.7[b]	31	1	0	1
9	11.0	51.2[b]	24	0	0	0
10[a]	11.7	52.6[b]	29	2	2	5
11	12.6	54.6[b]	18	0	0	0
12[a]	13.3	55.8[b]	39	5	0	5
13	13.5	56.3[b]	57	1	0	1
14	13.5	56.3[b]	20	0	3	0
15	16.0	60.4[b]	21	1	0	4
16	18.5	63.8[b]	27	0	0	2
17	18.6	63.9[b]	25	6	0	7
18	19.0	64.4[b]	48	6	5	9
19	19.4	64.9[b]	29	0	1	2
20[a]	21.1	66.7	52	0	0	2
21	21.2	66.9	37	0	0	0
22[a]	21.6	67.3	42	1	0	2
23	22.7	68.4	43	0	0	0
24	23.0	68.7	29	9	0	12
25[a]	23.9	69.5	31	4	3	4
26	26.0	71.3	20	6	0	4
27	27.5	72.4	24	0	0	1
28	28.7	73.2	57	4	0	4
29	34.7	76.8	53	0	0	0
30	35.9	77.4	23	4	0	2
31	40.9	79.6	40	3	0	3
32	43.6	80.6	46	0	0	2
33[a]	44.6	80.9	41	2	0	3
34	47.5	81.9	36	2	2	3
35[a]	57.2	84.5	50	10	0	9
36[a]	64.6	86.0	64	3	0	6

[a]Patients who received a concomitant antipsychotic drug.
[b]D_2 receptor occupancy level of < 65%.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, LAI = long-acting injectable, SAS = Simpson-Angus Scale.

Figure 1. Estimated Dopamine D_2 Receptor Occupancy in 36 Patients Receiving Risperidone Long-Acting Injectable (LAI)[a]



[a]Dotted lines represent 65% and 80% dopamine D_2 receptor occupancy levels, respectively.

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DISCUSSION

To our knowledge, this is the largest study to date that has investigated the dopamine D_2 receptor occupancy levels of risperidone LAI during the maintenance treatment of schizophrenia. Our results demonstrated that approximately 50% of subjects did not demonstrate continuous D_2 receptor occupancy ≥ 65%, which suggests that sustained D_2 receptor occupancy at or beyond the lower end of the therapeutic window reported for acute treatment (ie, 65%) may not always be necessary for patients in the maintenance phase of treatment.

The present findings corroborate the results of previous investigations examining the relationship between dopamine D_2 receptor occupancy and maintenance of clinical response in schizophrenia.[15,25] Uchida et al[15] have demonstrated that sustained blockade of dopamine D_2 receptor occupancy at ≥ 65% may not be necessary during maintenance treatment for individuals with schizophrenia receiving monthly administration of risperidone LAI (n = 7). In this study, while more than 50% of subjects showed D_2 receptor occupancy < 65% at trough on PET examination, none relapsed over a 1-year follow-up period. Mizuno et al[26] conducted a cross-sectional study and evaluated estimated D_2 receptor occupancy levels at peak and trough in 35 clinically stable patients with schizophrenia receiving risperidone or olanzapine. They demonstrated that approximately half the subjects did not achieve continuous blockade ≥ 65%; furthermore, roughly 10% did not attain the 65% threshold even at peak concentrations. Remington et al[25] compared the efficacy of extended but regular (alternate day) dosing of antipsychotics to once daily dosing in their double-blind randomized controlled trial (n = 35) and found no increased risk of symptom exacerbation, relapse, or rehospitalization in the extended dosing group over a 6-month follow-up period. Earlier investigations using intermittent antipsychotic dosing were associated with higher relapse rates; however, in these studies, antipsychotics were given at early signs of worsening and the resultant gaps in dosing were as long as months in duration.[27–29] It has been argued that intermittent, but regular, blockade of dopamine D_2 receptors with briefer, finite gaps has the potential to be both effective and safe, with fewer side effects. Summarizing, there are several lines of investigation suggesting that continuous blockade of dopamine D_2 receptor occupancy within the therapeutic window (ie, 65%–80%) may not always be necessary for maintenance treatment of schizophrenia.

This type of research is fueled by the goal of minimizing exposure to antipsychotic drugs given that their adverse effects are, at least in part, dose-dependent. Among them, EPS has identified as occurring with striatal D_2 occupancy > 80%.[12,30] Furthermore, animal studies have shown that continuous dopamine D_2 receptor blockade may increase the risk of tardive dyskinesia; for example, Turrone et al[31] demonstrated that continuous infusion of olanzapine in rats was associated with the increased risk of vacuous chewing movements, a model for tardive dyskinesia, while this was not observed when the same daily dose was administered via once daily injection. While the incidence of tardive dyskinesia has been reported as low as 0.7% with risperidone LAI,[8] duration of exposure was time-limited, that is 12 months, whereas in actual clinical practice, treatment is often decades in duration. Over and above movement disorders, an association between greater exposure to antipsychotic drugs and increased risk of sudden cardiac death has also been confirmed for both typical and atypical antipsychotic drugs.[14] In addition, previous PET studies have demonstrated that higher dopamine D_2 receptor occupancy is adversely associated with subjective well-being[13,32] and, according to a recent analysis of the data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, dopamine D_2 receptor occupancy > 80% may increase the risk of cognitive impairment.[11]

There are limitations to be noted in the present study. First, a period of clinical stability (ie, ≥ 6 months) required for inclusion in this study was arbitrary. Furthermore, our definition of clinical stability did not take into consideration the threshold level of psychopathology (eg, remission), nor did we address other features such as cognition or subjective response. In addition, any association between D_2 receptor occupancy and exact duration of clinical stability was not evaluated in the present study due to a lack of data. Second, it would have been ideal to evaluate the peak levels as well, considering that they may be more associated with side effects of antipsychotic drugs. However, side effects of antipsychotics have not been adequately explored in terms of peak versus trough levels of the compound (for instance, a PubMed search with keywords of *side effects*, *antipsychotics*, *peak*, and *trough* yields only 13 hits [last search: March 22, 2012], and none appears to be directly pertinent to this issue). Further, this evaluation would have needed an extra visit (ie, a few days after their regular visit), which is likely to have affected the recruitment process and the actual study conduct. This was a balanced reflection of practicality and ensuring representativeness of clinically stable patients with schizophrenia in real-world clinical settings. Third, we included patients who were concomitantly receiving another antipsychotic drug at bedtime for sedation purposes; however, this affected only 11 of the subjects in our sample and the mean ± SD chlorpromazine equivalent dose was as low as 45.5 ± 26.4 mg/d. Their effect on dopamine D_2 receptor occupancy the following day, however, would be expected to be of negligible significance. Indeed, the results remained almost the same when those concomitant doses were included in the estimation of dopamine D_2 receptor occupancy (Tables 2 and 3). Fourth, our focus on the dopaminergic system does not mean that the therapeutic benefits of antipsychotics are confined to this system. Clearly, the mechanisms by which these drugs effect their response is complex and we certainly do not exclude the effects of other systems such as the serotonergic[33,34] and cholinergic[35] systems. Finally, the cross-sectional design employed with this study limits any conclusions regarding a causal relationship between D_2 receptor occupancy levels

Table 3. Estimated D_2 Occupancy When Concomitant Antipsychotics are Taken Into Account[a]

Patient No.	D_2 Occupancy, %
1	29.0[b]
3	42.2[b]
7	55.0[b]
10	54.8[b]
12	66.9
20	68.9
22	71.0
25	71.3
33	82.4
35	86.8
36	88.2

[a]Concomitant doses were converted to risperidone long-acting injectable (LAI) equivalents and then added to the original risperidone LAI doses. See test for details.
[b]D_2 receptor occupancy level of < 65%.

and clinical outcome. For example, we found no significant association between dopamine D_2 receptor occupancy and EPS. Patients were not randomized to the doses assigned and therefore the doses that they were receiving were quite likely informed and limited by the actual clinical outcome. It is quite likely that a subgroup of patients is particularly sensitive to antipsychotics, and clinicians tend to prescribe lower doses to these patients in response to the observed clinical sensitivity; this may have blurred the relationship between D_2 receptor occupancy and EPS in this study. In fact, as we have already reported an association between dopamine D_2 receptor occupancy and antipsychotic side effects such as EPS and cognitive impairment elsewhere using large datasets,[11,30] we are of the opinion that adverse effects of antipsychotics, at least in part, depend on D_2 receptor occupancy. These preliminary findings must be replicated in well-designed prospective studies, and to this end, we are currently conducting such a trial to further investigate the significance of dopamine D_2 receptor occupancy in the maintenance treatment of schizophrenia.

In conclusion, our results suggest that sustained dopamine D_2 receptor occupancy levels ≥ 65% may not always be necessary for maintenance treatment with risperidone LAI in schizophrenia. While these preliminary findings must be confirmed in well-designed longitudinal studies, they have important implications for optimizing the dosing and/or dosing intervals of antipsychotics in clinically stable patients with schizophrenia to maximize effectiveness while reducing risk of side effects.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone long-acting injectable (Risperdal Consta).

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