Dose Reduction of Risperidone and Olanzapine and Estimated Dopamine D_2 Receptor Occupancy in Stable Patients With Schizophrenia: Findings From an Open-Label, Randomized, Controlled Study

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ABSTRACT

Background: While acute-phase antipsychotic response has been attributed to 65%–80% dopamine D_2 receptor blockade, the degree of occupancy for relapse prevention in the maintenance treatment of schizophrenia remains unknown.

Method: In this secondary study of an open-label, 28-week, randomized, controlled trial conducted between April 2009 and August 2011, clinically stable patients with schizophrenia (*DSM-IV*) treated with risperidone or olanzapine were randomly assigned to the reduction group (dose reduced by 50%) or maintenance group (dose kept constant). Plasma antipsychotic concentrations at peak and trough before and after dose reduction were estimated with population pharmacokinetic techniques, using 2 collected plasma samples. Corresponding dopamine D_2 occupancy levels were then estimated using the model we developed. Relapse was defined as worsening in 4 Positive and Negative Syndrome Scale-Positive subscale items: delusion, conceptual disorganization, hallucinatory behavior, and suspiciousness.

Results: Plasma antipsychotic concentrations were available for 16 and 15 patients in the reduction and maintenance groups, respectively. Estimated dopamine D_2 occupancy (mean ± SD) decreased following dose reduction from 75.6% ± 4.9% to 66.8% ± 6.4% at peak and 72.3% ± 5.7% to 62.0% ± 6.8% at trough. In the reduction group, 10 patients (62.5%) did not demonstrate continuous D_2 receptor blockade above 65% (ie, < 65% at trough) after dose reduction; furthermore, 7 patients (43.8%) did not achieve a threshold of 65% occupancy even at peak. Nonetheless, only 1 patient met our relapse criteria after dose reduction during the 6 months of the study.

Conclusions: The results suggest that the therapeutic threshold regarding dopamine D_2 occupancy may be lower for those who are stable in antipsychotic maintenance versus acute-phase treatment. Positron emission tomography studies are warranted to further test our preliminary findings.

Trial Registration: UMIN Clinical Trials Registry identifier: UMIN000001834

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Antipsychotic efficacy has been linked to dopamine D_2 receptor blockade,[1] a feature shared in common by all currently available antipsychotics. Previous positron emission tomography (PET) studies have consistently shown the presence of a therapeutic window of 65%–80% occupancy in the striatal dopamine D_2 receptors that is associated with optimal chance of therapeutic efficacy while minimizing risk of extrapyramidal symptoms in the treatment of schizophrenia.[2] However, it still remains unclear whether it is also necessary to maintain D_2 receptor occupancy to this degree for maintenance treatment. While the potential relevance of other neurotransmitters and receptors in schizophrenia should be acknowledged, a higher D_2 receptor occupancy with atypical antipsychotics has been associated at least partly with cognitive impairment,[3] negative subjective experience,[4] and hyperprolactinemia.[5] As such, the lowest possible D_2 receptor occupancy, even with atypical antipsychotics, represents a treatment goal to minimize side effects without sacrificing therapeutic efficacy. In fact, some studies using PET suggest sustained D_2 receptor blockade of ≥ 65% may not be necessary to maintain clinical wellness, although small sample sizes and use of long-acting injectable (LAI) antipsychotics need to be taken into account.[6,7]

In the real world, however, an access to PET is clearly limited. Thus, we have developed a model with which dopamine D_2 receptor occupancy levels for various antipsychotic drugs, including risperidone and olanzapine, can be estimated from their plasma concentrations.[8] In addition, recent advances in nonlinear, mixed-effects population pharmacokinetic methods have enabled us to estimate individual pharmacokinetic parameters for antipsychotic drugs, including peak and trough plasma drug concentrations, using 2 or more sparsely collected blood samples.[9] By combining these models, it is now possible to estimate D_2 receptor occupancy levels at any given point in time using the measurement of antipsychotic plasma concentrations at 2 separate random time points.[10]

Recently, we conducted a 28-week, randomized controlled trial to investigate the clinical impact of risperidone and olanzapine dose reduction in stable patients with schizophrenia and found that atypical antipsychotic dose reduction improved cognitive function and extrapyramidal symptoms without a worsening in psychopathology.[11] In the present study, on the basis of the above-mentioned technique, we evaluated estimated dopamine D_2 receptor occupancy levels at peak and trough before and after dose reduction of risperidone and olanzapine in clinically stable

Clinical Points

- Among clinically stable patients treated with risperidone or olanzapine, more than half did not demonstrate continuous dopamine D_2 receptor blockade above 65% after the dose was reduced by half. Nonetheless, only 1 patient experienced relapse during 6 months.
- The results suggest that while 65%–80% dopamine D_2 receptor occupancy with antipsychotics has been proposed to achieve optimal therapeutic response during acute-phase treatment of schizophrenia, sustained D_2 occupancy at 65% or more with antipsychotics may not be necessary for relapse prevention in the maintenance treatment of schizophrenia.

patients with schizophrenia. The objective of this article was to shed further light on optimal D_2 receptor occupancy with these 2 antipsychotics during the maintenance treatment of schizophrenia.

METHOD

Study Design

This secondary study was based on a multicenter, open-label, parallel-group, 28-week, randomized, controlled trial, conducted between April 2009 and August 2011,[11] to investigate the clinical impact of dose reduction of risperidone and olanzapine. Study procedures have been detailed elsewhere.[11] Briefly, patients were included if they were diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*),[12] receiving a stable dose of either risperidone > 2 mg/d or olanzapine > 5 mg/d as antipsychotic monotherapy for at least 3 months, and stable in terms of positive symptoms as defined by a score of ≤ 3 (mild) on the following 4 items of the Positive and Negative Syndrome Scale (PANSS)[13] Positive subscale, assumed to be representative of psychotic symptoms as well as disorganization: delusion (P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness (P6). Patients who met inclusion criteria were randomly assigned to either the reduction or maintenance group. In the reduction group, risperidone and olanzapine were reduced by 25% at baseline and week 4, followed by treatment with half the original dose over the next 24 weeks. For safety reasons, the dose was not reduced beyond the lower limit of the dose range recommended for maintenance treatment of schizophrenia, ie, risperidone 2 mg/d and olanzapine 5 mg/d.[14] Furthermore, 2 mg of risperidone has been suggested to be equivalent to 5 mg of olanzapine in terms of efficacy.[15] In the maintenance group, patients received the same regimen for the entire 28 weeks, while for each treatment arm, concomitant medications were kept constant throughout the study period.

The trial protocol was approved by the institutional review board at each participating site. All participants provided their written informed consent after full description of the study. This trial was registered at UMIN Clinical Trials Registry (UMIN000001834).

Table 1. Patients' Demographics in Reduction and Maintenance Groups[a]

	Reduction Group (n = 16)		Maintenance Group (n = 15)	
Characteristic	n or Mean	% or SD	n or Mean	% or SD
Male	8	50.0	9	60.0
Age, y	42.3	11.4	39.0	14.2
Outpatient	15	93.8	14	93.3
Duration of illness, y	18.1	11.5	11.4	12.3
Number of admissions	1.8	1.7	1.1	1.6
Number of patients taking risperidone	6	37.5	7	46.7
Number of patients taking olanzapine	10	62.5	8	53.3

[a]No significant differences in all values between the 2 groups.

Population Pharmacokinetic Analysis

Two plasma samples were taken for the measurement of risperidone active moiety (risperidone plus 9-hydroxyrisperidone) and olanzapine at 2 random time points. Plasma antipsychotic concentrations were assayed in heparinized plasma using a Perkin-Elmer LC/MS/MS (liquid chromatography with tandem mass spectrometry detection), with a limit of quantitation of 2 nmol/L (0.82 ng/mL), 5 nmol/L (2.13 ng/mL), and 7.5 nmol/L (2.3 ng/mL), respectively. The following information was also collected: time of last dose, dose frequency, dose amount, age, sex, race, weight, height, and smoking habits for the population pharmacokinetic analysis.

Using those 2 samples, we estimated plasma antipsychotic concentrations at peak and trough with the nonlinear mixed-effects population pharmacokinetic approach with NONMEM VII.[16,17] The nonlinear mixed-effects models for risperidone and olanzapine have been previously established using the data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies.[18,19] Patients in the CATIE provided plasma samples for the measurement of concentrations of risperidone active moiety and olanzapine at more than 1 time point. Individually specific pharmacokinetic parameters were obtained as Empirical Bayes Estimates by using these samples[16,17] through taking the following covariates into account: age for 9-hydroxyrisperidone[18] and sex, race, and smoking for olanzapine.[19] By using these pharmacokinetic parameters, we calculated the plasma antipsychotic concentrations at peak and trough for each individual. The model-predicted values of the plasma antipsychotic concentrations were then used to calculate dopamine D_2 receptor occupancy levels at the peak and trough for each individual.

Estimation of Dopamine D_2 Receptor Occupancy Levels

Using the predicted plasma concentrations of antipsychotics at peak and trough, we estimated corresponding dopamine D_2 receptor occupancy levels using the model we recently developed.[8] Briefly, D_2 receptor occupancy levels were calculated by incorporating the predicted plasma concentration of risperidone active moiety or olanzapine into the following one-site binding model: occupancy

Table 2. Clinical Psychopathology, Subjective Experience, and Extrapyramidal Symptoms in Reduction and Maintenance Groups[a]

	Reduction Group (n = 16)				Maintenance Group (n = 15)				Group Difference in Change,[b]
	Baseline		Change		Baseline		Change		
Outcome Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P* Value
PANSS									
Total	56.1	15.0	−4.8	10.4	55.5	13.2	−4.5	8.2	.92
Positive	10.8	3.5	−0.5	1.9	9.9	2.8	−0.9	2.3	.57
Negative	15.9	6.0	−1.9	2.9	17.0	7.0	−0.3	3.1	.16
General psychopathology	29.4	7.8	−2.4	7.3	28.7	6.2	−3.2	4.8	.74
CGI-S	2.8	1.0	−0.2	0.8	2.7	0.9	0.2	0.7	.14
CDSS Total	3.8	3.2	−1.5	2.9	3.3	2.2	−1.1	1.8	.62
SWNS Total	73.4	9.3	4.6	11.9	75.1	16.3	4.6	6.4	.99
DIEPSS Total	3.3	3.1	−0.8	1.4	2.7	2.1	0.1	1.5	.10

[a]Data represent last observation carried forward.
[b]No significant differences in all baseline values between the 2 groups by Student *t* test.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions–Severity of illness scale, DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SWNS = Subjective Well-being under Neuroleptic treatment Short form.

(%) = $a \times$ [plasma level/(plasma level + median effective concentration {EC_{50}})], where a is the maximum receptor occupancy attributable to the antipsychotic drug and EC_{50} is the estimated plasma concentration of the antipsychotic drug associated with 50% of receptor occupancy, which was obtained in the systematic review and pooled analysis (risperidone active moiety: $a = 88.0\%$, $EC_{50} = 4.9$ ng/mL; olanzapine: $a = 90.7\%$, $EC_{50} = 7.1$ ng/mL).[8]

Outcome Measures

The following assessments were performed at baseline and 28 weeks: the PANSS, the Clinical Global Impressions–Severity of illness scale (CGI-S),[20] the Calgary Depression Scale for Schizophrenia (CDSS),[21] the Subjective Well-being under Neuroleptic treatment Short form (SWNS),[22] and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).[23]

In this study, relapse was defined as a score of ≥ 4 (moderate) on at least 1 of the following 4 PANSS Positive subscale items: delusion (P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness (P6), all of which were better than moderate in severity at baseline.

Statistical Analyses

Baseline demographic and clinical characteristics were compared between the 2 groups by the Fisher exact test for categorical variables and the Student *t* test for continuous variables. The between-group differences in changes from baseline to endpoint in assessment scales were tested on an intention-to-treat basis by the Student *t* test using the last-observation-carried-forward (LOCF) method as our primary analysis. All analyses were conducted using the IBM SPSS Statistics version 19 (IBM Corporation, Armonk, New York), and a 2-tailed *P* value of < .05 was considered statistically significant.

RESULTS

Plasma concentrations of risperidone and olanzapine were available for 31 of 61 patients enrolled in the study, since we decided to add the measurements of plasma antipsychotic concentrations after having started the study. The patients were randomly assigned to the reduction group (n = 16) or the maintenance group (n = 15). In the reduction group, 2 patients (12.5%) discontinued for hospitalization due to relapse and water intoxication, respectively. In the maintenance group, 3 patients (20.0%) discontinued for poor adherence to medications, relapse due to poor adherence to medications, and sudden death due to unknown cause, respectively. Only 1 patient in each group met criteria for relapse. There was no significant difference in rate of study withdrawal or relapse between the 2 groups. Baseline demographic and clinical characteristics of the patients are shown in Tables 1 and 2. There were no significant differences in any baseline values or in changes in any clinical scale scores between the 2 groups (Tables 1 and 2).

Estimated plasma antipsychotic concentrations and estimated dopamine D_2 receptor occupancy levels at peak and trough in the reduction and maintenance groups are shown in Table 3. As expected, mean ± SD estimated D_2 receptor occupancy levels decreased following the dose reduction from 75.6% ± 4.9% to 66.8% ± 6.4% at peak and 72.3% ± 5.7% to 62.0% ± 6.8% at trough in the reduction group. In the reduction group, 10 patients (62.5%) did not demonstrate continuous D_2 receptor blockade at ≥ 65% (ie, < 65% at trough) after dose reduction; furthermore, 7 patients (43.8%) did not achieve a threshold of 65% occupancy even at peak (Figure 1). Despite these changes, only 1 patient (case 13) met relapse criteria after dose reduction (Figure 1).

DISCUSSION

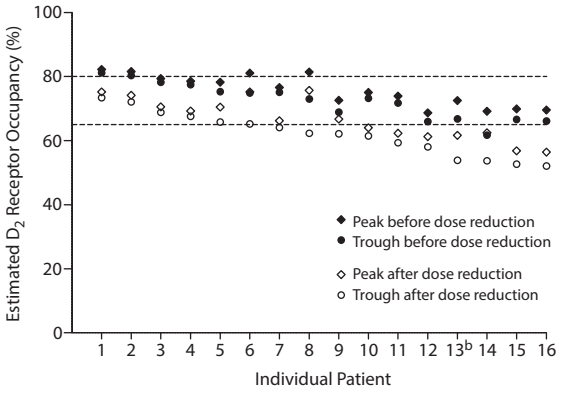
To our knowledge, this study is the first to examine estimated peak and trough dopamine D_2 receptor occupancy levels before and after risperidone and olanzapine dose reduction in clinically stable patients with schizophrenia. Our results indicate that more than half of the patients did not demonstrate a continuous D_2 receptor occupancy of ≥ 65% following risperidone and olanzapine dose reduction but remained clinically stable. These results suggest that

Table 3. Risperidone or Olanzapine Dose, Estimated Plasma Concentration,[a] and Estimated Dopamine D_2 Receptor Occupancy at Peak and Trough

	Reduction Group (n = 16)				Maintenance Group (n = 15)				Group Difference in Change,[b]
	Baseline		Change		Baseline		Change		
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P* Value
Dose, mg/d									
Risperidone	4.2	1.2	−1.9	0.8	4.0	1.4	0.0	0.0	**.002**
Olanzapine	13.8	5.4	−6.8	2.9	14.7	4.3	0.0	0.0	**<.001**
Estimated plasma concentrations, ng/mL									
Risperidone									
Peak	36.9	18.6	−17.3	10.6	27.6	17.5	0.0	0.0	**.010**
Trough	20.9	7.1	−9.6	4.5	15.1	11.9	0.0	0.0	**.003**
Olanzapine									
Peak	40.1	16.6	−19.7	8.8	51.0	31.8	0.0	0.0	**<.001**
Trough	35.0	15.0	−17.2	7.9	45.4	30.7	0.0	0.0	**<.001**
Estimated D_2 receptor occupancy, %									
Risperidone									
Peak	75.8	5.1	−7.1	2.0	72.5	5.2	0.0	0.0	**<.001**
Trough	70.1	5.3	−9.6	2.1	61.6	10.2	0.0	0.0	**<.001**
Olanzapine									
Peak	75.5	5.0	−9.9	2.3	77.3	5.2	0.0	0.0	**<.001**
Trough	73.6	5.8	−10.6	2.4	75.5	6.3	0.0	0.0	**<.001**
Risperidone plus olanzapine									
Peak	75.6	4.9	−8.9	2.5	75.1	5.6	0.0	0.0	**<.001**
Trough	72.3	5.7	−10.3	2.3	69.0	10.8	0.0	0.0	**<.001**

[a]Using population pharmacokinetic analysis.
[b]No significant differences in all baseline values between the 2 groups by Student *t* test. Bold represents $P < .05$.

Figure 1. Estimated Dopamine D_2 Receptor Occupancy at Peak and Trough Before and After Dose Reduction[a]



[a]Dotted lines represent 65% and 80% D_2 receptor occupancy.
[b]The patient experienced relapse.

sustained D_2 receptor occupancy at or beyond a threshold of 65% may not be necessary for at least some patients with schizophrenia to maintain clinical stability, which stands in contrast to well-replicated evidence involving acute-phase 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.[7,24–26] Uchida et al[7] have demonstrated that sustained blockade of 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 that study, while 4 of the 7 subjects showed D_2 receptor occupancy <65% at trough on PET examination, none relapsed during a 1-year follow-up period. Mizuno et al[24] 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 (n = 17) did not achieve continuous blockade at ≥65%; furthermore, roughly 10% (n = 4) did not attain the 65% threshold even at peak. Similarly, Ikai et al[25] found 19 of 36 clinically stable patients receiving risperidone LAI did not achieve continuous blockade at ≥65% in a cross-sectional study using estimated D_2 receptor occupancy. Furthermore, Remington et al[27] compared the efficacy of extended but regular (alternate day) dosing of antipsychotics to once-daily dosing in a double-blind, randomized, controlled trial (n = 35) and found no increased risk of symptom exacerbation, relapse, or rehospitalization in the extended dosing group during a 6-month follow-up period. Thus, there are now several lines of investigations suggesting that continuous blockade of D_2 receptor occupancy exceeding the therapeutic threshold of 65% may not always be necessary for maintenance treatment of schizophrenia.

Only 1 of 16 patients experienced relapse after dose reduction during 6 months in this study. This favorable result may reflect inclusion of clinically stable patients without significant positive symptoms (ie, scores ≤3 on P1, P2, P3, and P6). In addition, our study did not allow for a dose decrease beyond the lower limit of currently recommended doses (ie, risperidone 2 mg/d or olanzapine 5 mg/d). Our recent meta-analysis[28] revealed that the efficacy of moderately low and standard doses is comparable in preventing relapse in schizophrenia, whereas less than half the standard dose may increase risk of relapse. Thus, lower-dose strategies can be effective in maintenance treatment,

although the lowest threshold beyond which the risk of relapse rises remains to be elucidated. Moreover, the results of this study may be interpreted in a context of those of a recent intriguing work: Wunderink et al[29] followed patients with remitted first-episode psychosis for 7 years after an early dose reduction or discontinuation of antipsychotics and found that patients receiving antipsychotic reduction or discontinuation experienced greater rates of recovery and functional remission than those receiving antipsychotic maintenance treatment.

Limitations can be noted in the present study. First, the open-label design may have influenced results; more specifically, clinical outcomes in the reduction group may have been attributable to patients' and raters' expectation bias. Second, the follow-up period of 6 months could be too short to assess long-term outcomes, especially relapse rates, in schizophrenia. In fact, while 1 previous 6-month study[30] reported no increase in relapse following an approximately 25% dose reduction of olanzapine, a 1-year study[31] did demonstrate an increase in relapse after a 50% dose reduction of risperidone. In addition, previous longer-term randomized, controlled, dose reduction trials[32–34] of typical antipsychotics have shown that the relapse rates gradually increase even beyond 6 months, although the doses were reduced substantially to one-fifth or less in those studies. Therefore, our results regarding relapse should be conservatively interpreted. Third, the sample size was small, which did not allow us to separately analyze the data for risperidone and olanzapine, although the main purpose of the study was to descriptively report estimated D_2 occupancy at the peak and trough before and after dose reduction of antipsychotics. Fourth, dopamine D_2 receptor occupancy levels used in the present analysis were not actually measured but, instead, estimated based on the results from a pooled-analysis study. There may exist the patients who present high D_2 occupancy levels with low plasma antipsychotic concentrations, or vice versa. Moreover, the region of interest in 97% of the PET data used for the development of this prediction model was the striatum.[8] The findings in the present study need to be replicated in future investigations using high-affinity radiotracers that enable visualization and quantification of extrastriatal dopamine receptors as well. Fifth, we acknowledge the relevance of other neurotransmitter systems in schizophrenia treatment[35] although dopamine was the main focus in this article, and we still do not know the lowest possible threshold for D_2 receptor blockade. Sixth, a recent PET study found that stress induced dopamine release in schizophrenia,[36] which suggests that antipsychotic dose may need to be increased to prevent the risk of relapse under a stressful condition even in seemingly stable patients. Finally, medication adherence was assessed based on clinical interview at each visit without any objective measures such as pill count or electronic monitoring.

In conclusion, the findings from the present study suggest that optimal dopamine D_2 receptor occupancy levels appear to be lower in antipsychotic maintenance versus acute-phase treatment of schizophrenia. This clinical implication is significant vis-à-vis minimizing antipsychotic exposure, particularly given that guidelines generally recommend continuing the acute-phase dosage during maintenance treatment.[37] The present findings challenge this belief, although results need to be confirmed through double-blind, larger-scale, and longer-term studies.

Drug names: olanzapine (Zyprexa), risperidone (Risperdal and others).

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