Risperidone, 2 mg/day vs. 4 mg/day, in First-Episode, Acutely Psychotic Patients: Treatment Efficacy and Effects on Fine Motor Functioning

Marco C. G. Merlo, M.D.; Helene Hofer, Ph.D.; Walter Gekle, M.D.; Gregor Berger, M.D.; Joseph Ventura, Ph.D.; Ingrid Panhuber, Lic.Phil.; Gabriela Latour, Lic.Phil.; and Stephen R. Marder, M.D.

Background: The aim of this study was to examine differences in the improvement of clinical psychopathology and in fine motor functions at 2 doses of risperidone in first-episode, acutely psychotic patients.

Method: In a double-blind, fixed-dose study, 49 acutely psychotic, neuroleptic-naive patients who were admitted for the first time and who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder were randomly assigned to 2 or 4 mg/day of risperidone. Treatment efficacy was measured using the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, The Clinical Global Impressions scale, and the Social and Occupational Functioning Assessment Scale. Fine motor functions were assessed using a computerized device (the Vienna Test System) and were compared with those of a control group of 20 healthy subjects who were matched for age, gender, and educational level.

Results: Treatment with doses of 2 and 4 mg of risperidone daily significantly reduced positive ($p < .0001$) and negative ($p < .01$) symptoms at 8 weeks. Although there were no significant differences in motor movements as measured using the Barnes Akathisia Scale and the Simpson-Angus Scale, computerized fine motor assessment showed significantly less motor dysfunction in the 2-mg/day group at 8 weeks. No significant correlations to plasma concentration of active moiety were found for data on psychopathology and fine motor functions.

Conclusion: The 2 doses of risperidone did not differ in terms of clinical improvement, but the 2-mg/day dose produced fewer fine motor dysfunctions. These results suggest that a dose as low as 2 mg/day of risperidone may be effective for patients with first-episode psychosis.

(J Clin Psychiatry 2002;63:885–891)

Received Feb. 13, 2001; accepted Jan. 3, 2002. From the Hôpitaux Universitaires de Genève, Département de Psychiatrie, Chêne-Bourg (Genève), Switzerland (Dr. Merlo); the University of Berne, Berne, Switzerland (Drs. Hofer, Gekle, and Berger and Mss. Panhuber and Latour); and the University of California, Los Angeles (Drs. Ventura and Marder).

Supported by grant Nr. 3200-042561.94 from the Swiss National Science Foundation (Dr. Merlo) and by an unrestricted research grant from Janssen-Cilag AG (Switzerland) (Dr. Merlo). Janssen-Cilag also provided risperidone for the study and performed measurements of blood risperidone concentrations.

Presented in part at the 10th Biennial Winter Workshop on Schizophrenia, Feb. 5–11, 2000, Davos, Switzerland.

Dr. Merlo has received grant/research support from the Swiss National Science Foundation and Janssen-Cilag and has served on the speakers or advisory boards for Janssen-Cilag, Novartis, Lilly, Sanofi-Synthelabo, AstraZeneca, Lundbeck, and Bristol-Myers. Dr. Marder has been a consultant for Janssen, Lilly, Novartis, and Bristol-Myers; has received grant/research support from Janssen, Lilly, Novartis, AstraZeneca, and Pfizer; has received honoraria from Janssen, Bristol-Myers, Lilly, and Novartis; and has served on the speakers or advisory boards for Janssen, Lilly, Solvay, Bristol-Myers, Novartis, and Pharmacia & Upjohn.

The authors acknowledge statistical advice of M. Gex-Fabry, M.Sc., and the cooperation of the nursing staff of ward D1, University of Berne Psychiatric Hospital; the psychiatric research unit of Berne First Episode Psychosis Program, Berne; and the staff on ward 26 of the Psychiatric Hospital of Münsingen, Münsingen, Switzerland.

Corresponding author and reprints: Marco C. G. Merlo, M.D., Hôpitaux Universitaires de Genève, Département de Psychiatrie, Chêne-Bourg (Genève), Switzerland (e-mail: marco.merlo@hcuge.ch).

Since the early nineties, there has been a growing interest in the treatment of the early phases of psychosis.[1] The risk of tardive dyskinesia and other severe side effects has been used as an argument for selecting newer antipsychotic drugs for first-episode psychotic patients.[2] A recent open-label study found that patients with schizophrenia or schizophreniform disorder experienced alleviation of both positive and negative symptoms with a mean dose of 4.7 mg/day of risperidone.[3] In another open-label study of first-episode patients, risperidone was adjusted from a starting daily dose of 1 mg to a mean maximum dose of 4.16 mg and showed no difference in efficacy compared to a maximum daily dose of 3.95 mg haloperidol.[4] In addition, significantly fewer patients in the risperidone group needed concomitant administration of anticholinergic agents. In a recent multicenter, randomized, double-blind study of first-episode psychotic patients,[5] risperidone showed the same efficacy

as haloperidol, and there were no differences in efficacy between risperidone dosages < 6 mg/day and > 6 mg/day. However, the lower dose of risperidone caused fewer extrapyramidal side effects (EPS).

Studies using positron emission tomography[6,7] or single positron photon emission tomography[8] showed a high dopamine D_2 occupancy (> 80%) of risperidone at dosages of 6 mg/day in multiepisode patients. Recently, Nyberg and collaborators[9] found that reducing the risperidone dose from 6 mg/day to 3 mg/day resulted in a 72% (range, 53%–78%) occupancy of D_2 receptors, and they suggested 4 mg/day of risperidone as a suitable initial dose.

In first-episode psychotic patients, we hypothesized that 2 and 4 mg/day of risperidone would be in the therapeutic range, but that 4 mg/day of risperidone would cause EPS.[10] The aims of this study were to examine differences between 2 and 4 mg/day of risperidone on (1) symptom reduction, (2) extrapyramidal symptoms, and (3) fine motor functions in first-episode psychotic patients. Differences of "time to remission of positive symptoms" and "time to clinically meaningful improvement of global psychiatric symptoms" were also examined as well as correlations between psychopathology, fine motor functions, and plasma risperidone concentrations.

METHOD

Patients

All consecutive admissions were screened on a specialized unit for first-episode psychotic patients within the catchment area of the University of Berne [Switzerland] Psychiatric Institution (about 350,000 inhabitants). Of 63 patients who fulfilled inclusion criteria, 37 were entered into the study. Another sample of 15 first-episode patients from the Psychiatric Hospital of Münsingen (Switzerland) was studied with the same protocol on a general psychiatric ward. The recruitment and the overall standards of care for the acute treatment were similar in the 2 centers. There were no statistically significant differences ($p > .15$) between the 2 centers on the following sociodemographic and clinical variables: gender, diagnosis, and psychopathology as determined by Brief Psychiatric Rating Scale (BPRS)[11] total score and subscores as well as Scale for the Assessment of Negative Symptoms (SANS)[12] total score, Clinical Global Impressions-Severity of Illness (CGI-S)[13] score, and Social and Occupational Functioning Assessment Scale (SOFAS)[14] score. Each institution's human subjects protection committee approved the study. After a complete description of the study to the subjects, written informed consent was obtained.

Inclusion criteria were as follows: age between 16 and 40 years, IQ > 80, first psychotic episode, and DSM-IV diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.[14] Diagnosis was initially assessed using the International Diagnostic Checklist for DSM-IV[15] and verified using a semistructured diagnostic interview, the Schedules of Clinical Assessment in Neuropsychiatry.[16]

Study participation was limited to individuals who were acutely psychotic, i.e., they presented unusual thought content, hallucinations, and/or conceptual disorganization as defined by an expanded 24-item version of the BPRS that allows severity to be measured on a scale from 1 (not present) to 7 (extremely severe).[11] At least 1 of the following positive symptoms had to be of clinical significance (i.e., score equal to or higher than 4 [moderate]): unusual thought content (i.e., delusions), hallucinations, or conceptual disorganization. The BPRS total score at inclusion was in the range of 56 to 144 (median = 76). Urine samples for all patients were screened for street drugs and benzodiazepines before study entry. Patients were excluded from the study if they met DSM-IV criteria for substance dependence[14] or if drug tests were positive (except for cannabis and alcohol) or if medical examination, laboratory tests, or electroencephalogram revealed any physical illness in study subjects.

Of the 52 randomized patients, 3 were subsequently excluded because it was found that they had received haloperidol prior to hospitalization. None of the remaining 49 patients had ever received traditional high-potency antipsychotics, but 3 patients in the 2-mg/day group and 2 patients in the 4-mg/day group were being treated with levomepromazine, zuclopenthixol, or promazine for less than 4 days before study entry.

Table 1. Demographic and Clinical Characteristics of the Risperidone 2-mg/day and 4-mg/day Groups and the Control Group[a]

Variable	Risperidone 2 mg/d (N = 23)	Risperidone 4 mg/d (N = 26)	Control (N = 20)	p Value
Age, mean ± SD, y	23.2 ± 4.4	26.0 ± 7.2	26.6 ± 6.3	.56[b]
Education, mean ± SD, y	9.7 ± 1.2	9.5 ± 1.0	10.9 ± 1.5	< .01[b]
Gender				
Male	14 (60)	13 (50)	11 (55)	.75[c]
Female	9 (40)	13 (50)	9 (45)	
DSM-IV diagnosis				
Schizophrenia	13 (57)	16 (61)	…	.57[c]
Schizoaffective disorder	3 (13)	1 (4)	…	
Schizophreniform disorder	7 (30)	9 (35)	…	
Blood risperidone level, mean ± SD, ng/mL				
Day 28	16.1 ± 9.0	27.5 ± 12.5	…	NA
Day 56	11.7 ± 6.6	25.3 ± 19.1	…	NA

[a]Values shown as N (%) unless otherwise noted. Abbreviation: NA = not applicable.
[b]Kruskal-Wallis test.
[c]Exact chi-square test.

Table 2. Percentage of Patients Who Were Prescribed Concomitant Sedating Medication, by Week of Treatment

	Risperidone, 2 mg/d								Risperidone, 4 mg/d							
Medication	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
Lorazepam																
%	39.1[a]	26.1[a]	22.7	13.6	15.0	10.0	5.0	0.0	34.6	26.9	25.0	16.7	5.0	10.0	0.0	0.0
N/total N	9/23	6/23	5/22	3/22	3/20	2/20	1/20	0/20	9/26	7/26	6/24	4/24	1/20	2/20	0/19	0/19
Promazine																
%	69.6	56.5	45.5	40.9	35.0	30.0	30.0	20.0	69.2	69.2	45.8	37.5	40.0	15.0	10.5	15.8
N/total N	16/23	13/23	10/22	9/22	7/20	6/20	6/20	4/20	18/26	18/26	11/24	9/24	8/20	3/20	2/19	3/19

[a]One patient received diazepam.

The low-dose group (N = 23) was treated with 2 mg/day of risperidone and consisted of 14 males and 9 females. Thirteen patients in this group fulfilled DSM-IV criteria for schizophrenia; 7, for schizophreniform disorder; and 3, for schizoaffective disorder. In the standard-dose group (N = 26), 13 males and 13 females received 4 mg/day of risperidone. Sixteen patients in this group met criteria for schizophrenia; 9, for schizophreniform disorder; and 1, for schizoaffective disorder. The groups did not differ significantly in gender, age, level of education, duration of illness prior to study entry, or DSM-IV diagnoses (Table 1). There were also no significant differences in BPRS, SANS, CGI-S, and SOFAS scores between these 2 groups at baseline.

Controls

The control group for the fine motor function data consisted of 20 volunteers who had no history of a psychiatric or neurologic illness. They did not differ significantly in gender and age from the patients. Their level of education was slightly higher (Table 1).

Procedure

The trial had a double-blind, fixed-dose, parallel-group design with random assignment comparing 2 mg/day with 4 mg/day of risperidone for an 8-week period. During the first week, risperidone was gradually titrated to the patients' assigned study dosage starting with 0.5 mg/day. As concomitant medication for sedation, promazine (a sedating, short-acting antipsychotic) in doses up to 300 mg/day or lorazepam up to 10 mg/day were allowed. For EPS, biperiden could be administered in dosages up to 6 mg/day. Detailed information about comedication is provided in Table 2.

Treatment Efficacy Measures

The primary treatment efficacy variables were psychotic symptoms as derived from the expanded version of the BPRS.[11] In addition to BPRS total score, we computed scores for positive symptoms, negative symptoms, hostility-irritability, and depressive symptoms. Negative symptoms were also examined using the global score of the SANS.[12] Clinical improvement was defined as at least a 50% reduction from baseline in BPRS total score. Remission of positive symptoms was defined as not having BPRS scores that met inclusion criteria (i.e., 4 [moderate] to 7 [worse]) on any one of the following items: unusual thought content, hallucinations, or conceptual disorganization. Severity of illness was assessed using the CGI-S,[13] and social functioning was assessed using the SOFAS.[14]

All raters were trained on administration of the BPRS,[11] and a similar training program was used for the SANS. Additional BPRS interrater reliability data were collected using 15 videotaped interviews (each rater conducted 5 videotaped interviews), which were rated by all 3 raters. Intraclass correlation coefficients (ICCs)[17] were calculated for the BPRS total score and subscale scores, yielding values between 0.91 and 0.95. For the SANS total score, the ICC was 0.84.

For the assessment of fine motor functions, we used a computerized test battery: the Vienna Test System, Motor Performance Series (MLS).[18] Three tests were applied:

1. The Steadiness Test measures the ability to keep arm and hand in the same position independent of speed or strength. For this test, the subject holds a stylus into a hole in a metallic device. The number of touches (i.e., errors) is electronically detected.
2. The Line Tracking Test measures the precision of arm-hand movements. The patient puts a stylus into a track and moves through the track as fast as possible. Each touch of the wall (i.e., error) is counted electronically.
3. The Tapping Test measures wrist-finger speed. The patient taps with a stylus, as fast as possible, on a metallic square area for a predefined period of time. The number of hits is measured.

Test-retest reliability recently published for patients with Parkinson's disease[19] was r = 0.69 for number of errors on the Steadiness Test, r = 0.73 for number of errors on the Line Tracking Test, and r = 0.75 for hits on the Tapping Test.

Adverse events were continually monitored using the Simpson-Angus Scale,[20] the Barnes Akathisia Scale (BAS),[21] and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale.[22]

Table 3. Scores on the BPRS, SANS, CGI-S, and SOFAS at Baseline and Change in Scores at 8 Weeks for Patients Receiving 2 mg/day and 4 mg/day of Risperidone[a]

	Risperidone, 2 mg/d (N = 23)					Risperidone, 4 mg/d (N = 26)				
	Baseline		Change at 8 Weeks			Baseline		Change at 8 Weeks		
Rating Scale	Mean	SD	Mean	SD	Cohen d[b]	Mean	SD	Mean	SD	Cohen d[b]
BPRS										
Total[c]	76.2	15.2	–32.3*	15.1	2.1	83.3	20.1	–38.4*	16.9	2.1
Positive[c]	28.0	5.4	–15.4*	6.7	2.5	30.2	6.7	–16.7*	6.6	2.5
Negative[c]	8.6	4.0	–1.0*	2.7	0.3	9.9	3.6	–2.6*	2.8	0.8
Hostility-irritability[c]	15.6	7.2	–5.6*	5.7	0.9	18.5	6.6	–8.6*	4.9	1.5
Depressive[c]	14.7	4.6	–6.3*	2.8	1.7	14.4	5.0	–6.4*	4.2	1.4
SANS total global	13.0	5.6	–4.1*	4.6	0.8	14.0	5.1	–5.9*	5.4	1.1
CGI-S	5.9	0.5	–2.2*	1.4	2.1	6.0	0.6	–2.3*	1.3	2.2
SOFAS	28.0	13.1	25.6*	14.6	1.8	24.0	13.7	26.1*	19.4	1.6

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, SANS = Scale for the Assessment of Negative Symptoms, SOFAS = Social and Occupational Functioning Assessment Scale.
[b]Effect size: Cohen d = $|\mu_1-\mu_2|/\sigma$ within groups.
[c]Each BPRS item was rated from 1 (not present) to 7 (extremely severe).
*Significant difference from baseline to endpoint (paired t test: df = 22 for the 2-mg/day group, df = 25 for the 4-mg/day group, $p < .01$).

Blood samples were obtained in the morning, 12 to 16 hours after the last evening dose, so that trough concentration was measured. Because posology was kept constant from day 7 onward, steady state was assumed for parent compound and metabolite. Blood samples were drawn into heparin-treated glass tubes, and, after centrifugation, plasma was frozen at –20°C until analyzed. Plasma concentration of the "active moiety" (sum of risperidone and 9-hydroxyrisperidone) was determined by radioimmunoassay.[23]

Data Analysis

For group comparisons of categorical variables (clinical variables at baseline, safety variables, and amount of prescribed concomitant medication), the Fisher exact test or the exact chi-square test was performed. For ordinal or continuous variables (age, fine motor functions), the Kruskal-Wallis test with multiple comparison procedure was performed.[24] Associations between plasma concentrations and data on psychopathology and fine motor functions were computed using the Spearman correlation test.

Analyses of efficacy were defined according to the last-observation-carried-forward (LOCF) principle (endpoint being at 8 weeks). Changes in psychopathology from baseline to endpoint (week 8) were analyzed with repeated-measures analysis of variance (ANOVA) using the Huynh-Feldt correction for p values. Dose group and center were included as between-subjects factors. For testing differences between baseline and endpoint as well as for differences between groups, t tests were performed. Effect sizes were calculated using the Cohen d statistic.[25] Kaplan-Meier survival analysis was used to determine the time to remission of positive symptoms and time to global clinical improvement. Differences between the 2 treatment groups for time to remission of positive symptoms and time to global improvement were computed using the log-rank test. Two-tailed statistical tests were used throughout.

Nonparametric statistics were computed using StatXact[26] for exact p values, and the Statistical Analysis System (SAS)[27] was used for t tests, repeated-measures ANOVA, and survival analyses.

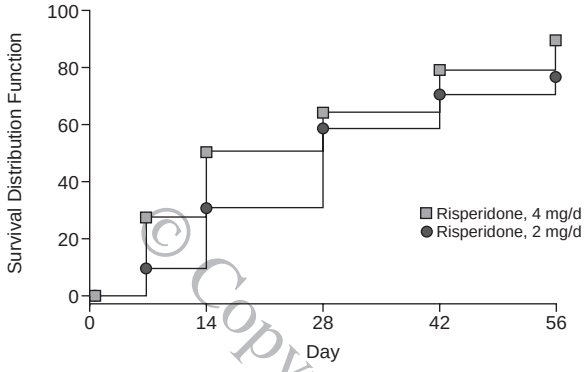
RESULTS

Treatment Efficacy

The 8-week study was completed by 39 of the 49 patients (79.6%). Three patients dropped out before week 4, 6 before week 6, and 1 before week 8. There were 3 dropouts (13%) in the low-dose group and 7 (27%) in the standard-dose group. Four (33%) of 12 patients from the specialized unit dropped out, whereas 6 (16%) of 37 from the general ward dropped out. Reasons for the 10 dropouts were noncompliance (N = 5), manic syndrome (N = 2), galactorrhea (N = 1), suicidality (N = 1), and aggressiveness (N = 1).

Psychopathology and social functioning of first-episode, acutely psychotic patients were analyzed for differences between the 2-mg/day and 4-mg/day treatment groups. Changes in BPRS total score, BPRS subscale scores, SANS symptoms scores, and CGI-S and SOFAS scores from baseline to trial completion (week 8 considering LOCF) yielded no significant difference between the 2-mg/day and 4-mg/day groups. In Table 3, the means and standard deviations as well as the effect sizes are reported. The effects sizes of within-group changes were strongest in both groups for BPRS positive score (Cohen d = 2.5 for both groups) and weakest for BPRS negative score (Cohen d = 0.3 for the 2-mg/day group and d = 0.8 for 4-mg/day group). Within-group comparisons showed significant differences between baseline values and those

Figure 1. Survival Function Estimates of Time to Remission of Positive Symptoms as Measured Using the Unusual Thought Content, Hallucinations, and Conceptual Disorganization Items of the Brief Psychiatric Rating Scale



at trial completion ($p < .0001$ for all data except $p < .01$ for BPRS negative score).

In a second step, we performed overall analyses of data from all timepoints (baseline and weeks 1, 2, 4, 6, and 8) applying repeated-measures ANOVA, with time as a within-subjects factor and group and center as between-subject factors. The computations were carried out for BPRS total score, BPRS subscale scores, and SANS symptoms scores. These analyses yielded significant time effects for all measures, but no statistically significant differences between groups (BPRS total score: $F = 0.15$, $df = 1,46$; $p = .70$; BPRS positive score: $F = 0.38$, $df = 1,46$; $p = .54$; BPRS negative score: $F = 0.02$, $df = 1,46$; $p = .90$; BPRS hostility-irritability score: $F = 0.18$, $df = 1,46$; $p = .67$; BPRS depressive score: $F = 0.33$, $df = 1,46$; $p = .57$; SANS total global score $F = 0.00$, $df = 1,46$; $p = .98$). Contrasts between each timepoint (baseline and weeks 1, 2, 4, 6, and 8) also revealed no significant differences between groups. No significant differences were found between the 2 centers. Computation of the same statistical tests including only the patients ($N = 44$) who had not received a treatment before study entry resulted in similar significance levels.

Time course of treatment efficacy was analyzed as time to remission of BPRS positive symptoms (Figure 1). At week 8, the probability of remission was 69.6% for the 2-mg/day group and 76.9% for the 4-mg/day group. In the 2-mg/day group, 3 (13%) of 23 patients dropped out before reaching remission and 4 patients had not met remission criteria at week 8. In the 4-mg/day group, 7 (27%) of 26 patients had an early dropout and 2 were not remitted at week 8. Statistical testing for group differences in "time to remission" of positive symptoms yielded no statistically significant difference between the 2 treatment groups ($\chi^2 = 1.65$, $df = 1$, $p = .20$; log-rank test). The analysis using the criterion of "meaningful clinical improvement" (i.e., 50% improvement in BPRS total score) yielded similar results. At week 8, the probability of improvement was 65.2% in the 2-mg/day group and 80.8% in the 4-mg/day group. Eight patients in the 2-mg/day group and 5 patients in the 4-mg/day group did not reach 50% improvement at week 8. Testing for between-group differences using the log-rank test showed no statistically significant difference for time to "meaningful clinical improvement" ($\chi^2 = 1.43$, $df = 1$, $p = .23$).

For patients not receiving comedication, Spearman correlation test yielded no significant relationship between the active moiety of risperidone plasma concentration and psychopathologic data (both measured at day 56) ($r_s < 0.12$, NS).

Adverse Events and Side Effects

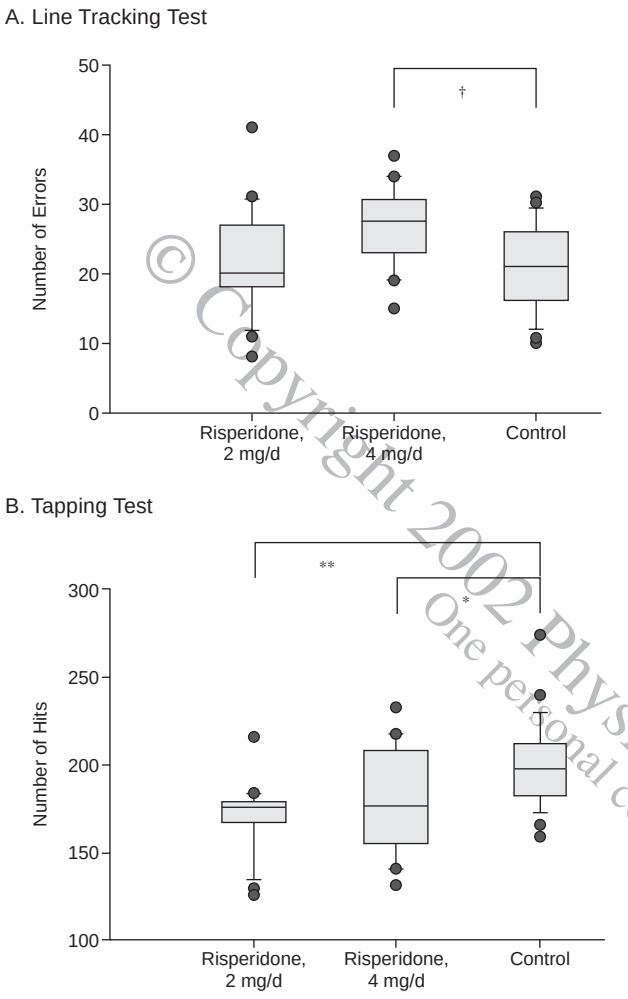
During the study, there were no serious adverse events. At week 8, 2 patients in the 2-mg/day group had a score of 3 or more ("strong") on the Simpson-Angus Scale compared with 3 patients in the 4-mg/day group. Also, 2 patients in the 2-mg/day group and 4 in the 4-mg/day group had a score of 2 or more ("moderate") on the BAS. The 2 treatment groups showed no statistically significant differences on these measures. For acute dystonic side effects, 2 patients in the 2-mg/day group and 3 patients in the 4-mg/day group received biperiden. At no point in time were there any statistically significant differences between treatment groups in the percentage of patients receiving concomitant medication for sedation (i.e., promazine or lorazepam) (Table 2).

The UKU Side Effect Rating Scale[22] revealed mild-to-moderate degrees of side effects for concentration difficulties, asthenia/lassitude/increased fatigability, sleepiness/sedation, failing memory, depression, tension/inner unrest, increased duration of sleep, emotional indifference, weight gain, and diminished sexual desire in about 30% to 50% of patients. Again, no statistically significant differences were found between the 2 groups on any of these items at week 4 or week 8. No subject was withdrawn from the trial because of an adverse event.

Fine Motor Functions

The values for the Steadiness Test, the Line Tracking Test, and the Tapping Test at week 8 were compared between the 2-mg/day group, the 4-mg/day group, and the control group of healthy volunteers using the Kruskal-Wallis test for overall testing and multiple comparison procedure for comparison of treatment versus control groups. Only patients who did not receive concomitant medication (i.e., promazine, lorazepam, or biperiden) 48 hours before testing were included. No significant differences were found between the 3 groups for the Steadiness Test, but significant differences were found for the Line Tracking Test ($p = .015$) and the Tapping Test ($p = .004$). Multiple comparisons for the Line Tracking Test showed a significant difference between the 4-mg/day group and

Figure 2. Box Plots of the Results of (A) the Line Tracking Test and (B) the Tapping Test for Patients Taking Risperidone, 2 and 4 mg/day, and Healthy Controls



†p < .05.
*p < .10.
**p < .05.

the control group (p < .05) only, whereas for the Tapping Test, the significance level was p < .05 for the comparison between 2-mg/day group and control group and p < .10 for the comparison between 4-mg/day group and control group. The results of the Line Tracking Test and the Tapping Test are displayed in Figure 2.

A Spearman correlation test yielded no significant relationship between the active moiety of risperidone plasma concentration (measured at day 56) and these fine motor function data (r_s < 0.14, NS).

DISCUSSION

This study evaluated 2 relatively low doses of risperidone for treating early psychosis. Forty-nine first-episode, acutely psychotic patients were randomly assigned to 2 mg/day or 4 mg/day of risperidone under double-blind conditions. Treatment efficacy measures showed highly significant changes from baseline to trial completion. Between-group comparisons yielded no significant differences for positive and negative symptoms or for global symptoms and community functioning scores. In addition, the need for concomitant medication for sedation and extrapyramidal symptoms was the same for both groups. Adverse effects measured using standard clinical rating scales also did not differ in the 2 treatment groups.

We interpret our findings as supporting the hypothesis that first-episode patients may be treated with lower dosages than are commonly needed in chronically psychotic patients. The lower dose of 2 mg/day of risperidone is also lower than those suggested by open-label studies[3,4] and a recent double-blind study.[5] Further support for this approach to antipsychotic treatment of first-episode psychotic patients is suggested by our finding of few study dropouts and a lack of serious adverse events.

Interestingly, not only did the level of improvement on clinical measures show no significant difference between the 2 groups, but also no difference in the time to meaningful clinical improvement or remission of positive symptoms. As shown in previous studies,[28,29] we have replicated the findings that, for antipsychotic drugs, it is important to wait a certain time for evaluating antipsychotic effect. After 4 weeks, probability of remission of positive symptoms was 32% in the 2-mg/day group and 48% in the 4-mg/day group. However, it increased to 69.6% in the 2-mg/day group and 76.9% in the 4-mg/day group at week 8. Thus, our strategy of early intervention with a newer antipsychotic drug suggests that the time to remission may be even shorter than it was in previous studies.[30,31] In addition, this study confirms that early changes of dose or changes to another antipsychotic may make little pharmacologic sense.

Fine motor functions were also measured to corroborate the clinical assessments of motor side effects. The Line Tracking Test showed advantages for the 2-mg/day group. Scores on the Tapping Test did not significantly differ between the 2 dose groups, but both groups showed a significant difference compared with healthy subjects. In the precision of arm-hand movement, there may be an advantage of 2 mg/day of risperidone compared with 4 mg/day. These data confirm the study by Casey,[10] who found EPS even at low doses in cebus monkeys treated with risperidone. Our results also lend support to positron emission tomography results[6,7,9] favoring a dosage under 4 mg/day of risperidone. Since the relationship between the level of D_2 receptor occupancy and the risk of tardive dyskinesia remains unclear, it seems warranted to avoid levels of dopamine blockade that may lead to side effects. Fine motor dysfunctions may be early signs of risk and should be considered for defining optimal dosage.

Plasma concentration was not related to psychopathologic data or fine motor functioning, confirming the results of a recent study by Spina and collaborators.[32]

One important limitation to this study was our need to manage patients with sedating antipsychotics and benzodiazepines for agitation. The use of sedating antipsychotic drugs for acutely psychotic patients was the accepted clinical practice at our sites. Although we attempted to minimize this practice, the use of these agents may have affected the measurement of fine motor movements.

CONCLUSION

Risperidone, 2 mg/day and 4 mg/day, led to similar clinical improvement in first-episode, mainly neuroleptic-naive, acutely psychotic patients. The time to remission of positive symptoms and the improvement of global psychopathology also did not differ between these groups. However, 2 mg/day of risperidone produced fewer fine motor dysfunctions. These results support the proposed strategy of early application of low dosages of an atypical antipsychotic in first-episode patients. It also supports the need for an individualized duration of treatment during the acute phase. We recommend 2 mg/day as an initial minimal effective dose of risperidone in first-episode psychosis and propose at least 6 to 8 weeks of observation time for evaluation of its efficacy.

Drug names: biperiden (Akineton), diazepam (Valium and others), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal).

REFERENCES

1. Keshavan MS, Schooler NR. First-episode studies in schizophrenia: criteria and characterization. Schizophr Bull 1992;18:491–513
2. McGorry P, Edwards J. Early Psychosis Training Pack. Macclesfield, England: Gardiner-Caldwell Communications Limited; 1997
3. Kopala LC, Good KP, Honer WG. Extrapyramidal signs and clinical symptoms in first-episode schizophrenia: response to low-dose risperidone. J Clin Psychopharmacol 1997;17:308–313
4. Keshavan MS, Schooler NR, Sweeney JA, et al. Research and treatment strategies in first-episode psychosis: the Pittsburgh experience. Br J Psychiatry 1998;172(suppl 33):60–65
5. Emsley RA, and the Risperidone Working Group. Risperidone in the treatment of first-episode psychotic patients. Schizophr Bull 1999;25:721–730
6. Nyberg S, Farde L, Eriksson L, et al. 5-HT_2 and D_2 dopamine receptor occupancy in the living human brain: a PET study with risperidone. Psychopharmacology (Berl) 1993;110:265–272
7. Kapur S, Remington G, Zipursky RB, et al. The D_2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. Life Sci 1995;57:103–107
8. Busatto GF, Pilowsky LS, Costa DC, et al. Dopamine D_2 receptor blockade in vivo with the novel antipsychotics risperidone and remoxipride: an ^{123}I-IBZM single positron photon emission tomography (SPET) study. Psychopharmacology (Berl) 1995;117:55–61
9. Nyberg S, Eriksson B, Oxenstierna G, et al. Suggested minimal effective dose of risperidone based on PET-measured D_2 and 5-HT_{2A} receptor occupancy in schizophrenic patients. Am J Psychiatry 1999;156:869–875
10. Casey DE. Behavioral effects of sertindole, risperidone, clozapine and haloperidol in cebus monkeys. Psychopharmacology 1996;124:134–140
11. Ventura J, Green MF, Shaner A, et al. Training and quality assurance with the Brief Psychiatric Rating Scale: "The Drift Busters." Int J Methods Psychiatr Res 1993;3:221–244
12. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Iowa: The University of Iowa; 1984
13. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare; publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
15. Hiller W, Zaudig M, Mombour W. IDCL: International Diagnostic Checklists for ICD-10 and DSM-IV. Seattle, Wash: Hogrefe & Huber Publishers; 1996
16. World Health Organization Division of Mental Health. WHO SCAN Advisory Committee. SCAN Schedules of Clinical Assessment in Neuropsychiatry, Version 1.0. Geneva, Switzerland: World Health Organization; 1992
17. Bartko JJ, Carpenter WT. On the methods and theory of reliability. J Nerv Ment Dis 1979;163:307–317
18. Schuhfried G. The Vienna Test System. Motor Performance Series. Available at: http://www.schuhfried.co.at. Accessed June 2002
19. Ringendahl H. Normierung der Motorischen Leistungsserie (MLS) für dei Messung feinmotorischer Störungen beim Morbus Parkinson. Nervenarzt 1998;69:507–515
20. Simpson GM, Angus JWS. Drug-induced extrapyramidal disorders. Acta Psychiatr Scand Suppl 1970;212:17–19
21. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
22. Scandinavian Society of Psychopharmacology Committee of Clinical Investigations (UKU). The UKU Side Effect Rating Scale: scale for the registration of unwanted effects of psychotropics. Acta Psychiatr Scand 1987;76(334, suppl):81–94
23. Huang M-L, Van Peer A, Woestenborghs RJ, et al. Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. Clin Pharmacol Ther 1993;54:257–268
24. Siegel S, John Catellan N Jr. Nonparametric Statistics for the Behavioral Sciences, 2nd ed. New York, NY: McGraw-Hill Book Company; 1988
25. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillside, NJ: Lawrence Erlbaum Associates; 1988
26. Cytel Software Corporation. StatXact 4. Cambridge, Mass: Cytel Software Corporation; 1998
27. SAS Institute. SAS/STAT User's Guide, Version 6. Cary, NC: SAS Institute; 1990
28. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. Arch Gen Psychiatry 1991;48:739–745
29. Kinon BJ, Kane JM, Johns C, et al. Treatment of neuroleptic-resistant schizophrenic relapse. Psychopharmacol Bull 1993;29:309–314
30. MacMillan JF, Cros TJ, Johnson AL, et al. Short-term outcome in trial entrants and trial eligible patients. Br J Psychiatry 1986;148:128–133
31. Lieberman J, Jody D, Giesler S, et al. Time course and biological correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993;50:369–376
32. Spina E, Avenoso A, Facciolá G, et al. Relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and clinical response in patients with schizophrenia. Psychopharmacology 2001;153:238–243