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Extrapyramidal side effects with risperidone and haloperidol at comparable D2 receptor occupancy levels

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Abstract

Risperidone is an antipsychotic drug with high affinity at dopamine D2 and serotonin 5-HT2 receptors. Previous clinical studies have proposed that risperidone's pharmacologic profile may produce improved efficacy for negative psychotic symptoms and decreased propensity for extrapyramidal side effects; features shared by so-called 'atypical' neuroleptics. To determine if routine risperidone treatment is associated with a unique degree of D2 receptor occupancy and pattern of clinical effects, we used [^{123}I]IBZM SPECT to determine D2 occupancy in subjects treated with routine clinical doses of risperidone ($n = 12$) or haloperidol ($n = 7$). Both risperidone and haloperidol produced D2 occupancy levels between approximately 60 and 90% at standard clinical doses. There was no significant difference between occupancy levels obtained with haloperidol or risperidone. Drug-induced parkinsonism was observed in subjects treated with risperidone (42%) and haloperidol (29%) and was observed at occupancy levels above 60%. Based on these observations, it is concluded that 5-HT2 blockade obtained with risperidone at D2 occupancy rates of 60% and above does not appear to protect against the risk for extrapyramidal side effects.

Keywords: I-123-IBZM; SPECT; Neuroleptics; Antipsychotics; Schizophrenia

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1. Introduction

Risperidone is an antipsychotic drug with purported atypical features. In-vitro studies with risperidone have demonstrated nanomolar affinities at several neurotransmitter receptors, most notably serotonin 5-HT2 and dopamine D2 (Janssen et al., 1988; Leysen et al., 1988). In preclinical animal studies (Janssen et al., 1988; Megens et al., 1988) and in preliminary human studies (Roose et al., 1988; Castelao et al., 1989; Mesotten et al., 1989), risperidone was shown to have antipsychotic efficacy with few extrapyramidal side effects. In placebo-controlled studies (Borison et al., 1992; Chouinard et al., 1993; Marder and Meibach, 1994), risperidone had beneficial effects on positive and negative symptoms of psychosis, decreased dyskinetic movements, and at least at 'low' doses produced less parkinsonism than standard doses of haloperidol.

The biochemical mechanisms for the atypical features of risperidone are not clearly understood. Clozapine, which is regarded as the standard atypical neuroleptic, has been shown to produce high degrees of 5-HT2 receptor occupancy and low degrees of D2 occupancy at clinically effective doses in comparison with typical neuroleptics (Brücke et al., 1992; Farde et al., 1992; Pilowsky et al., 1992; Nordström et al., 1993, 1995; Scherer et al., 1994; Pickar et al., 1996). This profile may in part explain the improvement in negative symptoms and the reduced frequency of extrapyramidal side effects observed with clozapine treatment.

In order to determine if the putative reduced propensity for parkinsonism observed with risperidone is related to an atypical profile of D2 receptor blockade, we employed [^{123}I]IBZM SPECT to examine the relationship of D2 receptor occupancy with several clinical variables in patients receiving standard clinical doses of risperidone and haloperidol.

2. Methods

2.1. Subjects

Patients were hospitalized at the National Institute of Mental Health, Neuropsychiatric Research Hospital at St. Elizabeths in Washington, D.C. Patients with chronic psychotic syndromes according to DSM-IV criteria (American Psychiatric Association, 1994) that required neuroleptic treatment were accepted for the study. All patients had been chronically ill and had been treated with a variety of prior medications. The study subjects were unwilling or unable to be observed free of medications, and therefore quantitative clinical ratings in a drug-free condition were not available. Admission medications and other characteristics of the psychotic subjects at admission are displayed in Table 1. There were no significant differences between subjects treated with haloperidol and risperidone with regard to age or illness duration. Following admission, those patients not already taking risperidone or haloperidol were given these medications after tapering of admission medications over a 2-week period. The treating psychiatrist adjusted the dosage of medication until the patients were felt to be clinically stable and the neuroleptic dosage was then held constant for at least 3 weeks prior to SPECT scanning.

On the day of the SPECT scan, blood levels of neuroleptics were obtained. Haloperidol levels were determined by the National Psychopharmacology Laboratory (Knoxville, Tennessee) with high-pressure liquid chromatography. Levels of parent risperidone and its active metabolite, 9-OH-risperidone, were determined by National Medical Services (Willow Grove, Pennsylvania) with high-pressure liquid chromatography.

On the day of the SPECT scans the subjects were rated independently by two psychiatrists with the Psychiatric Symptom Assessment Scale (PSAS, Bigelow and Berthot, 1989), the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1984) and the Modified Abnormal Involuntary Movement Scale (AIMS, Wyatt, 1993). The mean of the two raters' scores was utilized for data analysis. The intraclass correlation coefficient for the two raters for the PSAS was 0.93; that for the SANS was 0.87; and that for the AIMS was 0.81 ($P < 0.001$ for all scales). The Modified Abnormal Involuntary Movement Scale includes scales for chorea, dystonia, tremor,

Table 1
Subject characteristics at admission

Subject	Age	Sex	Diagnosis	Illness duration	Admission medications	Baseline parkinsonism
H1	30	M	US	12	Haloperidol, benztropine, imipramine	2[a]
H2	36	F	DS	16	Haloperidol, benztropine	2[a]
H3	41	M	US	20	Haloperidol, benztropine	0
H4	26	M	RS	7	Haloperidol, trihexyphenidyl, verapamil	0
H5	36	M	US	19	Fluphenazine, benztropine, propranolol	0
H6	39	M	US	20	Loxitane, lorazepam	0
H7	44	M	SA	21	Perphenazine, lithium, benztropine	2[a]
R1	36	M	US	20	Clozapine, sertraline	2
R2	33	M	SA	10	Clozapine, clonazepam, lithium, valproic acid	6
R3	51	F	US	32	Clozapine, metoprolol	0
R4	53	F	PNOS	14	Risperidone, paroxetine, desipramine, carbamazepine, lisinopril, procyclidine	0
R5	40	M	PS	28	Haloperidol	0
R6	49	M	US	27	Haloperidol, propranolol, pindolol	2
R7	31	M	US	12	Haloperidol, benztropine	2[a]
R8	28	M	US	9	Trifluoperazine, benztropine	0
R9	34	M	US	17	Clozapine, valproic acid	1[a]
R10	39	M	US	16	Thioridazine, benztropine	2[a]
R11	33	M	SA	8	Risperidone	0
R12	51	M	CPS	32	Risperidone, valproic acid, paroxetine	2

[a] Subject did not have two of three parkinsonian signs.
Abbreviations: H, haloperidol; R, risperidone; US, undifferentiated schizophrenia; DS, disorganized schizophrenia; RS, residual schizophrenia; PS, paranoid schizophrenia; SA, schizoaffective; PNOS, psychosis not otherwise specified.

bradykinesia, rigidity and tremor. None of the patients in this study experienced acute dystonia with either of the neuroleptics. Patients who received scores for chorea and dystonia had these symptoms chronically as part of the tardive dyskinesia syndrome. The sum of the chorea and dystonia subscales was therefore used as a measure of the severity of dyskinetic movements to be correlated with scan outcome measurements. The sum of ratings for tremor, bradykinesia and rigidity was used as a measure of the severity of drug-induced parkinsonism. In order to avoid including patients who may have had tremor, bradykinesia or rigidity for other reasons, patients were considered to have clinically significant drug-induced parkinsonism only if they had ratings for two of the three parkinsonian signs. Characteristics of subjects at the time of scan are presented in Table 2.

Baseline modified AIMS ratings for parkinsonism at admission were available and are listed in Table 1. At admission, patients who were scanned on haloperidol did not differ significantly from those scanned on risperidone in terms of ratings for parkinsonism (0.87 ± 1.73 vs. 1.42 ± 1.07, respectively — these and all subsequent results expressed as mean $\pm$ S.D.).

2.2. I-123 IBZM SPECT procedure

All subjects provided written informed consent

Table 2
Subject characteristics at scan

Subject	Dose (mg/kg)	Dose (mg)	Diagnosis	Other medications	Parkinsonism at scan	Occupancy (%)
H1	0.21	20	US	None	2*	72
H2	0.14	10	DS	Isoniazid	6	66
H3	0.26	20	US	Benztropine	0.5*	69
H4	0.03	4	RS	Trihexyphenidyl, verapamil	2*	74
H5	0.08	6	US	None	0	85
H6	0.17	20	US	Benztropine	0	96
H7	0.05	5	SA	Lithium, valproic acid	3.5	91
R1	0.08	6	US	Phenytoin	0	46
R2	0.02	3	SA	Clonazepam	12	62
R3	0.03	2	US	Lisinopril	1.5*	96
R4	0.02	1.5	PNOS	Proxitene, desipramine, carbamazepine, lisinopril, procyclidine	0	56
R5	0.06	6	PS	None	1*	99
R6	0.04	4	US	Benxtrophine, propranolol, pindolol	3	99
R7	0.05	6	US	None	0	97
R8	0.05	6	US	None	4	71
R9	0.12	10	Us	None	2*	98
R10	0.03	2	US	Benztropine	10	69
R11	0.04	4	SA	Benztropine	19	83
R12	0.02	2	CPS	Valproic Acid, paroxetine	0	87

[a] Subject did not have two of three parkinsonian signs.
Abbreviations: H, haloperidol; R, risperidone; US, undifferentiated schizophrenia; DS, disorganized schizophrenia; RS, residual schizophrenia; PS, paranoid schizophrenia; SA, schizoaffective; PNOS, psychosis not otherwise specified.

for the SPECT protocol which had been approved by the National Institute of Mental Health Institutional Review Board. On the day prior to SPECT scanning and for 3 subsequent days the subjects received five drops of Lugol's solution by mouth in order to prevent uptake of the radioligand into the thyroid gland. The synthesis of [^{123}I]IBZM and assessment of radiochemical purity have been described previously (Kung and Kung, 1989; Knable et al., 1995). The psychotic subjects received approximately 185 MBq of [^{123}I]]IBZM (mean = 182 MBq; range: 148–189 MBq) intravenously at approximately 13.00 h. Patients reclined in the gantry of the CERASPECT camera (Digital Scintigraphics, Waltham, MA) with their canthomeatal lines aligned with a laser beam parallel to the transverse plane of the gamma camera. Scans were obtained in step-and-shoot mode for 120 projections. A high sensitivity collimator with 11.5-mm FWHM resolution was employed. Scatter correction and filter settings for reconstruction were as previously reported (Knable et al., 1995). A 30-min SPECT scan was obtained from 90 to 120 min after injection of the radioligand. This time period was assumed to represent the equilibrium binding of IBZM based on previously reported time–activity curves for IBZM (Knable et al., 1995; Wolf et al., 1996). Sixteen normal control subjects (five females and 11 males; mean age 28.8 ± 7.8 years) without evidence of medical or psychiatric disorders were also recruited for [^{123}I]IBZM SPECT scans. Normal controls also received approximately 185 MBq of [^{123}I]IBZM (mean = 189 MBq; range: 178–267 MBq) and a series of 15-min scans over a 4-h period were obtained according to previously reported methods (Knable et al., 1995; Wolf et al., 1996). Scans obtained between 90 and 120 min were analyzed for comparison to the psychotic subjects.

2.3. Image analysis

Prior to image analysis, each SPECT scan was rotated to predetermined landmarks in three orthogonal planes in order to control for variations in subject positioning. The central slice in the transverse plane was aligned so that the interhemispheric fissure was vertical. Likewise, a line connecting the orbital surface of the frontal lobe and the tentorial notch was made horizontal for the central sagittal slice and the interhemispheric fissure was made vertical in the central coronal slice of the coronal.

Regions of interest (ROIs) used for analysis were of uniform size (10 cm^2). The ROIs were placed on five consecutive slices (1.67-mm thick) containing cerebellum (to define non-specific binding) and on five slices containing the most prominent signal from the basal ganglia (to determine total binding). The average counts per minute in the ROIs from the five slices were recorded and were corrected for decay. The ratio of specific to non-specific IBZM binding, (basal ganglia − cerebellum)/cerebellum, was calculated as an outcome measurement proportional to the equilibrium binding potential ($BP = B_{max}/K_d$) according to previously reported assumptions (Laruelle et al., 1994; Knable et al., 1995).

2.4. Data analysis

The specific/nonspecific binding ratio of haloperidol and risperidone treated patients was compared to that of normal controls with Student's *t*-test. Binding of IBZM was also expressed relative to the control group in order to calculate an estimate of D2 receptor occupancy according to the following:

$$\text{Occupancy} = \left[1 - \left(\frac{BPs}{BPn}\right)\right] \times 100 \quad (1)$$

where *BPn* is the mean value obtained from the normal control group and *BPs* is the value obtained from individual psychotic subjects. The value of *BPn* was 2.17 ± 0.63.

Correlations between clinical variables and estimated D2 occupancy levels were sought with Pearson's product–moment test. For heuristic purposes, an attempt was made to fit occupancy levels data to a saturation hyperbola model:

$$\text{Occupancy} = \frac{Occ_{\max} \times F}{Ki + F} \quad (2)$$

where Occ_{max} is a parameter representing maximal receptor occupancy, F is the concentration of neuroleptic in blood or neuroleptic dose and Ki is a parameter representing the concentration of neuroleptic, or the neuroleptic dose, necessary to produce 50% of maximal occupancy. Non-linear curve fitting was performed with the SigmaPlot software (Jandel Scientific, Corte Madera, CA).

3. Results

3.1. Relationship of neuroleptic dose and serum concentration

The mean dose of haloperidol was 0.13 ± 0.09 mg/kg (range: 4–20 mg/day). The mean serum haloperidol concentration was 4.33 ± 2.25 ng/ml. Administered dose was not significantly correlated with serum blood level ($r = 0.66$, $P = 0.16$). The mean dose of risperidone was 0.05 ± 0.03 mg/kg (range: 1.5–10 mg/day). The mean sum of risperidone and its principal metabolite in the plasma, 9-OH-risperidone, was 31.9 ± 25.2 ng/ml. Risperidone dose was significantly correlated with the serum concentration of the sum of the two species ($r = 0.80$, $P = 0.003$).

3.2. Mean values of IBZM binding and correlation with clinical variables

The IBZM SPECT data obtained from controls and neuroleptic-treated patients are displayed in Fig. 1. The mean values of IBZM specific/non-specific binding ratio were significantly lower in haloperidol- (0.45 ± 0.26) and risperidone- (0.49 ± 0.40) treated patients compared to controls ($P < 0.001$). This suggests that routine clinical doses of risperidone produce D2 receptor occupancy levels comparable to those of typical neuroleptic drugs. There was no significant difference between risperidone-treated and haloperidol-treated patients ($t = -0.25$, $P = 0.81$).

There were no significant correlations between D2 receptor occupancy level, dose, or blood level

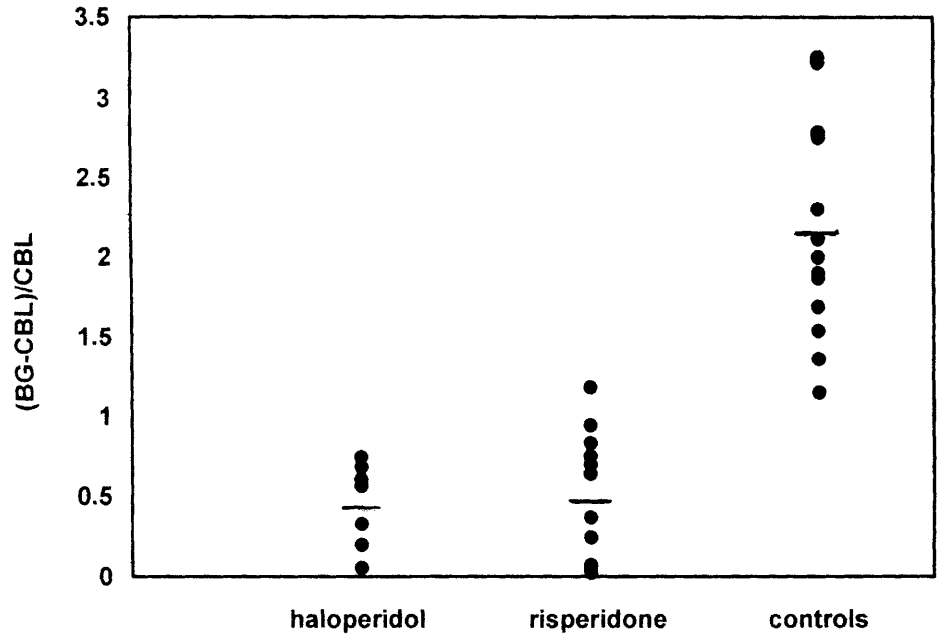

Fig. 1. Ratio of specific to non-specific IBZM binding in neuroleptic-treated patients and normal controls. Both haloperidol- and risperidone-treated subjects had significantly lower striatal IBZM binding than controls (Student's $t = -8.78$ and -8.22, respectively; $P < 0.001$ for both comparisons). There was no significant difference between haloperidol- and risperidone-treated subjects.

and clinical measures of movement disorder, positive symptoms and negative symptoms in haloperidol-treated patients. D2 receptor occupancy levels observed in risperidone-treated patients were negatively correlated with AIMS scores ($r = -0.73$, $P = 0.05$) and with the chorea subscale ($r = -0.83$, $P = 0.05$), suggesting that choreiform movement disorders can be suppressed by high levels of D2 receptor blockade. There were no other significant correlations between occupancy levels and measures of parkinsonism, positive symptoms or negative symptoms. There were no significant correlations between dose or blood levels of risperidone with any clinical measure.

3.3. Relationship of neuroleptic dose and blood level to D2 receptor occupancy

Although the lack of low D2 receptor occupancy levels obtained in this study precludes drawing precise conclusions concerning the value of K_i, the asymptotic portion of the hyperbola is easily demonstrated. The predicted value for maximal occupancy in haloperidol-treated patients was approximately 93% ($r^2 = 0.91$) when blood level was used as the independent variable and 80% ($r^2 = 0.89$) when dose was the independent variable.

In risperidone-treated patients, the predicted value for maximal occupancy was 83% ($r^2 = 0.66$) when blood level was used as the independent variable and was 86% ($r^2 = 0.62$) when dose was the independent variable. The relationship of risperidone dose to D2 receptor occupancy is illustrated in Fig. 2.

3.4. Relationship of D2 occupancy and drug-induced parkinsonism

Patients scanned while taking haloperidol had

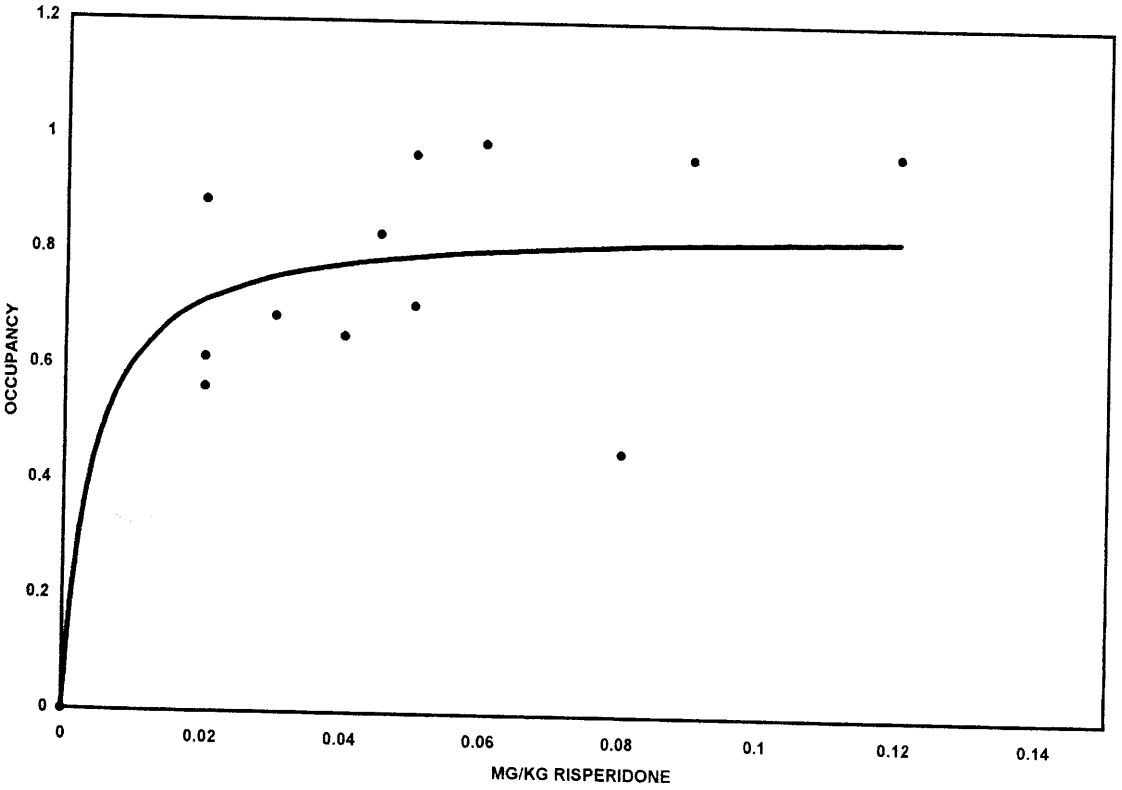

Fig. 2. Relationship of risperidone dose and D2 occupancy. Maximal occupancy was estimated to be 86% ($r^2 = 0.62$).

significantly higher ratings for parkinsonism compared to baseline ratings (2.1 ± 2.2 vs. 0.9 ± 1.1, $P = 0.03$). Likewise, patients scanned while taking risperidone had significantly higher ratings for parkinsonism compared to baseline ratings (3.6 ± 4.8 vs. 1.4 ± 1.7, $P = 0.05$). Two of the seven subjects taking haloperidol (29%) and five of the 12 subjects taking risperidone (42%) were considered to have clinically significant drug-induced parkinsonism. As illustrated in Fig. 3, parkinsonism was observed at occupancy levels greater than 60%. There was no significant difference in mean occupancy levels between those subjects who developed parkinsonism and those who did not ($F = 0.60$, d.f. = 15, $P = 0.63$). It was not clear that the presence or absence of anticholinergic medications or other concomitant medications influenced the assessment of parkinsonism in this small sample. Four of the 12 patients taking risperidone were receiving anticholinergic medications. Three of these four had among the highest ratings of parkinsonism and had occupancy levels of 70% or above. If these patients had n been receiving anticholinergic medications, th ratings of parkinsonism would have been m likely worse and their occupancy levels ev higher.

These data suggest that at high levels of D occupancy the high degree of 5-HT2 antagonis afforded by risperidone does not appear to pr vent the emergence of extrapyramidal side e fects.

4. Discussion

As other groups have observed with haloper dol (Farde et al., 1998; Wolkin et al., 1989; Brück et al., 1992; Scherer et al., 1994; Nyberg et a 1995; Klemm et al., 1996) and in smaller sample of subjects treated with risperidone or other atyp ical neuroleptics such as olanzapine (Nyberg e al., 1993; Kapur et al., 1995), high levels of D2 receptor occupancy are obtained with standar clinical doses of either type of neuroleptic. This suggests that commonly used clinical doses o

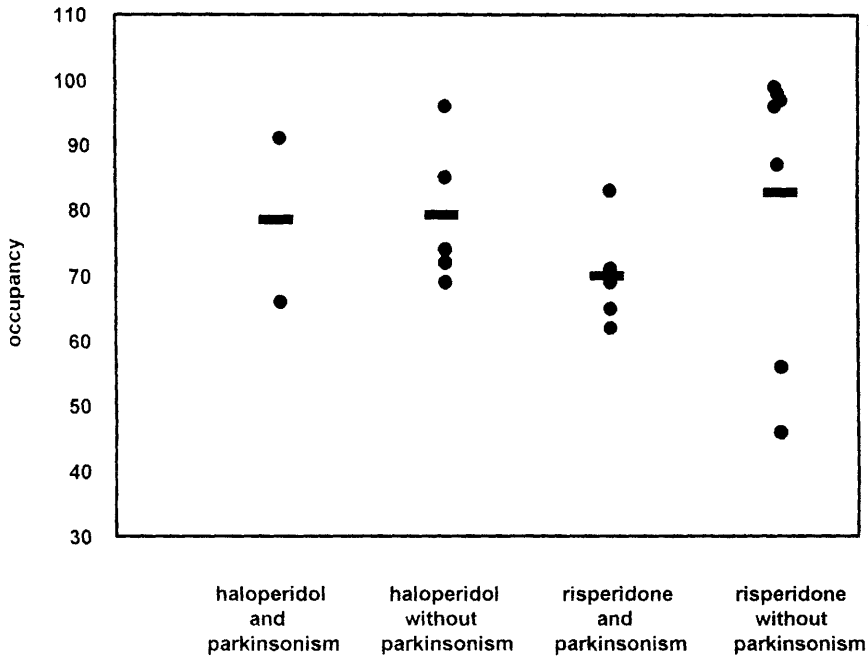

Fig. 3. D2 receptor occupancy levels in patients with and without parkinsonism. There was no significant difference between groups ($F = 0.60$, d.f. = 15, $P = 0.63$).

neuroleptic drugs may be excessive or that mechanisms other than the level of striatal D2 receptor blockade are important for optimal antipsychotic efficacy.

We observed a high frequency of parkinsonism in subjects treated with haloperidol and with risperidone at comparable levels of D2 occupancy. The frequency of parkinsonism with risperidone treatment observed in this study was higher than that reported in prior studies of the clinical effectiveness of risperidone. Despite the putative benefit of 5-HT2 antagonism in the prevention of extrapyramidal side effects of neuroleptics, our data suggest that 5-HT2 antagonism obtained with typically employed doses of risperidone is insufficient to confer this benefit, at least at levels of D2 occupancy above a threshold of 60–70%. Possible explanations for this discrepancy may be found in the chronicity of our subjects' illnesses and prior neuroleptic treatment and in the higher doses of risperidone they received in the current study compared to those in prior studies.

Previous neuroimaging studies have suggested that parkinsonism occurs after D2 receptor occupancy exceeds 80% (Farde et al., 1992). The observation in the present study of drug-induced parkinsonism at occupancy levels above 60% may again be due to unusual characteristics of the present cohort, to differences produced by the inherent error of the IBZM SPECT method, or perhaps by differences in the pharmacological behavior of the PET and SPECT radioligands. However, the observation of parkinsonism at or above 60% occupancy levels is very consistent with prior pathological (Jellinger, 1986; Gibb, 1992) and neuroimaging studies (Frost et al., 1993; Marek et al., 1996) of patients with Parkinson's disease that suggest symptoms become clinically manifest following the loss of as little as 50% of nigrostriatal neurons.

We observed significant negative correlations between D2 receptor occupancy level with risperidone and clinical ratings for chorea. These results are consistent with previous observations that neuroleptics are able to suppress involuntary dyskinetic movements seen in tardive dyskinesia and other choreiform movement disorders (van Woert, 1983). It is interesting to note that one clinical study with risperidone reported a beneficial effect of risperidone treatment on the severity of dyskinesias that was not observed with haloperidol (Chouinard et al., 1993).

It should also be pointed out that several methodological problems may have influenced the conclusions of this study. Absolute values for occupancy may reflect the error inherent in the IBZM SPECT technique, which has previously revealed variability in clinical populations of 15–25% (Knable et al., 1995; Wolf et al., 1996). The interpretation of preliminary results from this study should also be made with caution, since patients treated with haloperidol and risperidone may not have been well matched for prior extrapyramidal side effects, a standardized clinical outcome was not used, computation of occupancy level from individual neuroleptic-free scans was not possible and many of the patients were studied while receiving concomitant medications. We have also not been able to measure extra-striatal D2 receptor occupancy, or D2 receptor occupancy in mesolimbic portions of the striatum with IBZM SPECT. Occupancy of these receptors may reveal different relationships with clinical efficacy than those reported for the striatum as a whole.

In summary, this study has shown that high levels of D2 receptor occupancy and the emergence of parkinsonism are observed with routine clinical doses of both haloperidol and risperidone. This suggests that risperidone may be more similar to 'typical' neuroleptics than previous experience would suggest, at least above a certain threshold of D2 receptor occupancy. Future studies with prospectively determined neuroleptic doses designed to produce 50–60% occupancy in the absence of other medications will be necessary to more fully elucidate the relationship between D2 occupancy and clinical efficacy and the possibility of atypical risperidone effects.

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