Iodine-123-Iodobenzamide SPECT Assessment of Dopamine D_2 Receptor Occupancy in Risperidone-Treated Schizophrenic Patients

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The recently introduced neuroleptic, risperidone, was expected to block fewer dopamine D_2 receptors than typical neuroleptics (e.g., haloperidol), but at comparable potency. The aim of this study was to evaluate the degree of dopamine D_2 receptor occupancy in relation to the neuroleptic dosage and to correlate the findings with the presence of extrapyramidal symptoms (EPS). Additionally, the data were compared to previous iodobenzamide (IBZM) SPECT findings in patients treated with other neuroleptics, haloperidol and clozapine. **Methods:** In 20 patients with schizophrenia [*Diagnostic and Statistical Manual of Mental Disorders (Third Edition-Revised)*] treated with mean daily doses of risperidone ranging from 0.029 to 0.128 mg/kg body weight, SPECT was performed 2 hr after intravenous injection of 185 MBq ^{123}I-IBZM, a selective dopamine D_2 receptor ligand. Striatal IBZM binding was assessed by calculating a striatal/frontal cortex ratio, expressed as a percentage of the control value. **Results:** Selective dopamine D_2 receptor binding of the ligand was reduced in all treated patients, with binding values ranging from 7% to 68%. The degree of occupancy displayed an exponential dose-response relationship ($r = -0.86$; $p < 0.0001$). The slope of the curve was between those of haloperidol and clozapine but was closer and more similar in shape to the curve of haloperidol. Extrapyramidal symptoms were observed in 8 of 20 patients with binding values between 7% and 47%. However, there was no clear relationship between the degree of receptor occupancy and the presence of EPS. **Conclusion:** The findings suggest an exponential dose-response relationship between the daily dosage of risperidone and the dopamine D_2 receptor occupancy. The blockade of specific striatal IBZM binding found under therapy with risperidone is between those of haloperidol and clozapine. The dose-response curve for risperidone, however, shows greater similarity to that of haloperidol.

Key Words: iodine-123-iodobenzamide SPECT; schizophrenia patients; risperidone; extrapyramidal symptoms

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According to the "dopamine hypothesis" (*1*), positive symptoms of schizophrenia are due to hyperactivity of the dopaminergic system. The widely accepted concept is that occupancy of dopamine D_2 receptors is both essential and sufficient for a drug to have antipsychotic properties (*2*). As previously reported, dopamine D_2 receptors can be studied in vivo using SPECT applying ^{123}I-iodobenzamide (IBZM). IBZM is a benzamide derivative developed for SPECT that has been shown to bind reversibly with high affinity and high specificity to striatal D_2 receptors (*3,4*). The occupancy of striatal D_2 receptors by various classic neuroleptics in schizophrenic patients has been demonstrated (*2*). By means of IBZM and SPECT, the occupancy of D_2 receptors in patients receiving treatment with neuroleptics has been described in several studies (*5,6*).

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The dopamine hypothesis has been challenged with the advent of atypical antipsychotics. Clozapine, the archetypal drug in this group, displays remarkable clinical efficacy (*7*), with a low propensity to induce catalepsy in rats (*8*). Clozapine has been shown to have only weak D_2 receptor antagonistic properties in vitro, in contrast with its high affinity for a variety of other neuroreceptors (*9*).

Recently, new antipsychotics have been developed, among them risperidone, and have been licensed for clinical use. They are at least as effective as conventional antipsychotics but, like clozapine, have a decreased capacity to induce catalepsy in rats (*10*). The pharmacological profile underlying the atypical properties of risperidone has not yet been fully evaluated, and it is unclear whether the clinical efficacy is also related to blocking of dopamine D_2 receptors.

The aim of this study was to evaluate the degree of D_2 occupancy in relation to the neuroleptic dosage and to correlate the findings with the presence of extrapyramidal symptoms (EPS). Additionally, the data were compared to our previous findings of IBZM SPECT in patients receiving treatment with haloperidol and clozapine.

MATERIALS AND METHODS

Twenty patients with schizophrenia [*Diagnostic and Statistical Manual of Mental Disorders (Third Edition-Revised)* (DSM-III-R) (*11*)] (12 women, 8 men; age range 19–63 yr) who were treated with mean daily doses of risperidone ranging from 0.029 to 0.128 mg/kg body weight (2–8 mg) were examined. Concomitant medication is listed in Table 1. No patient received any medication the day before or the day of IBZM examination. In the case of diazepam, the last medication was given at least 1 wk before the SPECT scan. None of these drugs is supposed to influence the dopaminergic system or the binding of IBZM to the dopamine D_2 receptor. The duration of illness varied between the first onset of symptoms a few weeks before and more than 10 yr before examination. Five of the patients were also examined in a drug-naive state. For assessment of EPS, the EPS rating scale was applied by two psychiatrists blinded to the findings of the IBZM SPECT study.

For SPECT image acquisition, we used a triple-headed gamma camera equipped with high-resolution fanbeam collimators (Prism 3000; Picker, Cleveland, OH). The acquisition parameters comprised a rotational radius of 13 cm or less, a 20% energy window centered on 159 keV, 120 projection angles over 360° and a 128 × 128 matrix with a pixel width of 2.11 mm in the projection domain. Data collection started 120 min after injection and lasted for approximately 30 min (45 sec/projection). The projection images were reconstructed by filtered backprojection. Then a three-dimensional, counting rate-dependent, postprocessing filter (Wiener filter) with a modular transformation function specific for ^{123}I was applied. For uniform attenuation correction, Chang's first-

TABLE 1
Patients' Mean Daily Dosages of Risperidone and Background Corrected Values Expressed as Percentage Binding of Controls

Patient no.	Daily dosage of risperidone (mg/kg body weight)	Concomitant medication	(S − BG)/BG (% binding)
Before treatment	0.000	None	119
Before treatment	0.000	Doxepin	108
Before treatment	0.000	None	94
Before treatment	0.000	None	92
Before treatment	0.000	None	91
1	0.029	None	68
2	0.029	None	63
3	0.037	Diazepam (occasionally)	63
4	0.039	None	31
5	0.041	None	63
6	0.041	None	57
7	0.041	Amitryptiline	41
8	0.042	None	41
9	0.053	None	41
10	0.058	None	44
11	0.059	None	41
12	0.067	Doxepin	56
13	0.075	None	42
14	0.093	None	21
15	0.100	None	31
16	0.100	None	28
17	0.100	None	20
18	0.100	None	7
19	0.120	None	21
20	0.128	None	33

S − BG/BG = striatum − background/background.

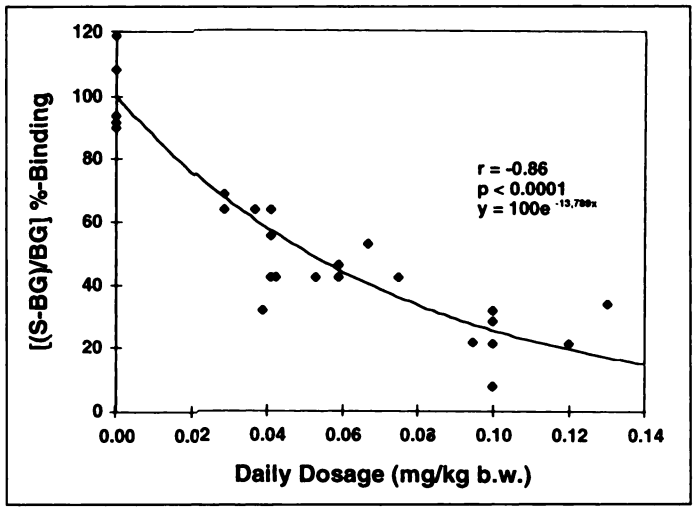

FIGURE 1. Dose-response relationship between striatal D_2 receptor occupancy [(S − BG)/BG percentage binding] and daily dose of risperidone (mg/kg body weight).

order method was used. Images were uniformly resliced by drawing a line connecting the anteriormost aspect of the frontal pole to the posteriormost aspect of the occipital pole, which approximates the line connecting the anterior and posterior commissures. To assess specific tracer uptake in the striatum, we used the region of interest (ROI) technique. Mean specific activity in basal ganglia regions was calculated by subtracting the mean counts per pixel in the frontal cortex as background (BG) from the mean counts per pixel in the basal ganglia region (S) and dividing the result by the mean counts per pixel in the background [(S − BG)/BG]. Templates were used for defining the striatal ROIs. The size and the shape of the templates were established and optimized using data from a control group. The nonspecific background activity was estimated by drawing an ROI around the frontal cortex. In each patient, data were evaluated in the two consecutive transverse slices showing the highest tracer accumulation in the basal ganglia. Results are given as arithmetic mean of the two slices. For statistical analyses, analysis of variance, regression analyses (least-squares method) and Student's t-test were used. Monoexponential fitting was applied to all data. All values were normally distributed. Differences were considered statistically significant when $p < 0.05$.

Data were compared to the results of a previously published study (*6*) of IBZM SPECT in patients receiving treatment with haloperidol and clozapine.

All data were expressed as a percentage of normal binding with a 100% value of [(S − BG)/BG] = 0.95 for the risperidone-treated group and 0.52 for the haloperidol- and clozapine-treated groups, respectively, which were established by a control population. The difference from the normal values (0.95 versus 0.52) was due to the different technical equipment used in the risperidone study (triple-headed camera, Prism 3000; Picker) and that used in the previously performed haloperidol/clozapine study (dual-headed camera, Rota II; Siemens, Iselin, NY; this system was replaced by the Picker system). Measurements in controls and a phantom were used to ensure that data obtained using both approaches were comparable. The control groups used for this study consisted of 10 healthy, age-matched subjects for each camera system, which were examined to establish the threshold of IBZM binding to the dopamine D_2 receptor, above which subjects were considered to display normal binding. Two of them underwent imaging procedures on both gamma cameras. Additionally, five patients of the risperidone-treated group had baseline scans presenting with values consistent with the normal values established in the control group. The phantom used was a striatal/basal ganglia phantom developed by the department of medical physics (University of Munich, Germany) containing four chambers (caudate right/left and putamen right/left) and a background chamber that could be filled separately. The experiments were performed by filling the phantom with different basal ganglia/background ratios and performing identical measurements on both cameras. The results of the phantom studies and for the two control subjects scanned on both cameras were used to confirm the comparability of the camera systems. The expression of the main outcome measure as a percentage eliminates the different absolute ratios of both cameras, since an individual control group was available. Therefore no corrections to the data were made.

RESULTS

Table 1 gives a summary of the subjects' medical characteristics and IBZM SPECT findings. The dopamine D_2 receptor binding of the ligand was reduced in all patients {[(S − BG)/BG] percentage binding = 7–68%} during therapy with risperidone. All examinations of untreated patients showed normal values. Figure 1 displays the (S − BG)/BG percentage binding values, reflecting dopamine D_2 receptor binding in relationship to the daily dosage of risperidone. The degree of occupancy of the dopamine D_2 receptors presented an exponential dose-response relationship ($r = -0.86$; $p < 0.0001$). Figure 2 shows similar data previously obtained in patients treated with haloperidol and clozapine. The remarkable linear dose-response curve for clozapine-treated patients reflects the lower D_2 receptor occupancy induced by this compound. Even at the maximum doses of clozapine, D_2 receptors in basal ganglia remained unoccupied. A close inspection of the risperidone data

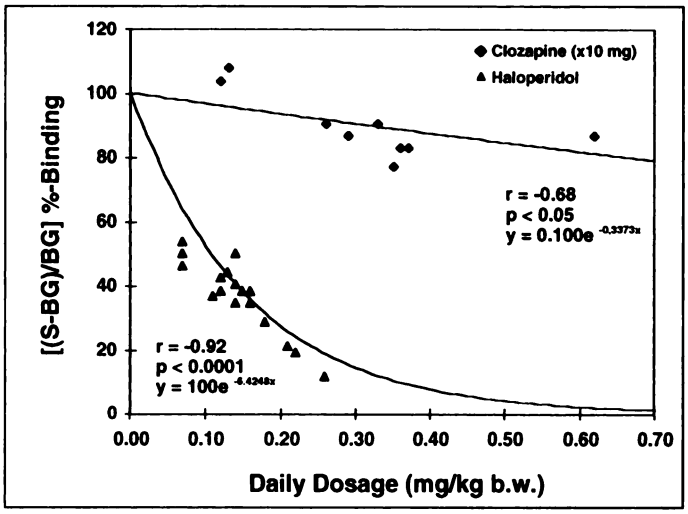

FIGURE 2. Dose-response relationship between striatal D_2 receptor occupancy [(S − BG)/BG percentage binding] and daily dose of haloperidol and clozapine (mg/kg body weight).

and similar data obtained using haloperidol and clozapine suggests that the degree of specific striatal IBZM binding induced by risperidone is between that of patients treated with typical and atypical neuroleptics and is clearly lower than binding in nonmedicated patients and controls. The slope of the curve was closer to that of haloperidol. Qualitatively, the pattern of ^{123}I-IBZM binding displayed remarkable similarity to that found in patients receiving typical neuroleptic treatment.

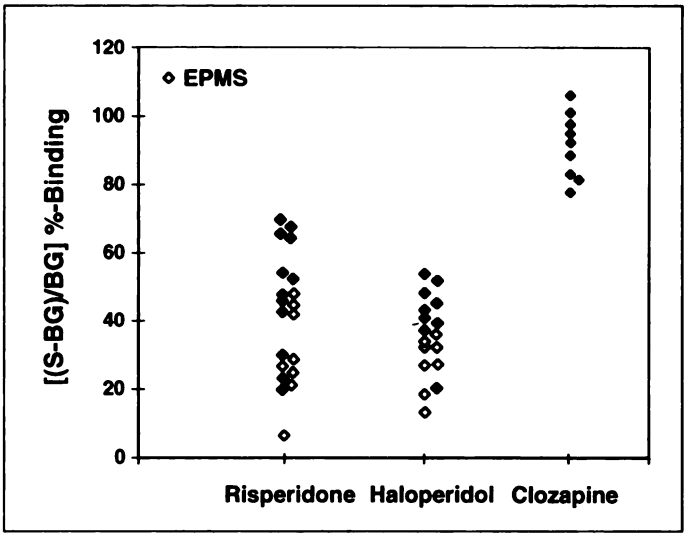

FIGURE 3. Relationship between striatal D_2 receptor occupancy [(S − BG)/BG percentage binding] and presentation of extrapyramidal symptoms (EPMS).

Extrapyramidal symptoms were observed in eight patients showing (S − BG)/BG percentage binding values between 7% and 47% (Fig. 3). However, there was no clear relationship between the degree of receptor occupancy and the presence of EPS. These findings suggest that patients treated with risperidone display no direct relationship between striatal D_2 occupancy and the presence of EPS. Our previous study of haloperidol-treated patients showed a threshold value of IBZM binding to the D_2 receptor of 40%, which means that patients usually displayed EPS presenting a D_2 receptor occupancy of 60% or higher. Similarly, patients receiving risperidone treatment showing D_2 receptor binding higher than 47% (occupancy <53%) exhibited no EPS. However, some of the risperidone-treated patients presenting with binding values below this threshold also displayed no EPS. Figure 4 shows a typical image in patients before and after treatment with different doses of risperidone.

DISCUSSION

The findings of our study indicate an exponential dose-response relationship between the daily dosage of risperidone and the dopamine D_2 receptor occupancy. The blockade of specific striatal IBZM binding is between those produced by haloperidol and clozapine. Extrapyramidal symptoms were observed in a remarkable subset of 40% of patients. However, there was no clear relationship between the degree of receptor occupancy and the presence of EPS.

Due to their propensity of inducing extrapyramidal side effects mediated by dopamine D_2 receptor occupancy, most neuroleptics are usually referred to as typical antipsychotics. In contrast, atypical neuroleptics are those that have fewer or no extrapyramidal side effects in humans and do not produce catalepsy in animals (*12*). Clozapine was the first neuroleptic to meet these criteria and to have a strong antipsychotic potency (*13*). In our previous study (*6*), the occupancy of striatal D_2 receptors in patients receiving treatment with clozapine was significantly lower than that in patients taking typical high-potency neuroleptics such as haloperidol but was not lower than that in neuroleptic-free subjects. These results are consistent with SPECT studies reported by other groups (*5,14,15*). In addition, Farde et al. (*16*) reported a range of 38%–63% D_2 receptor occupancy in five patients taking clozapine using PET and ^{11}C-raclopride. Similarly, the values of our patients were significantly lower than those of patients treated with conventional doses of typical antipsychotics. The occupancy of the D_2 receptor has been suggested to mediate the antipsychotic effects

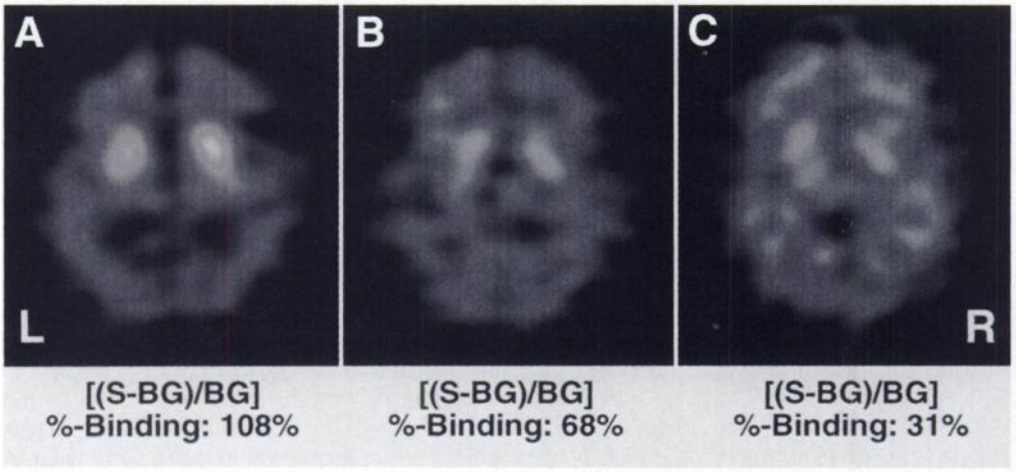

FIGURE 4. Iodine-123-IBZM SPECT images of D_2 receptor binding at equilibrium. (A) Drug-naive schizophrenic patient. (B) Schizophrenic patient receiving treatment with risperidone at daily dosage of 37 μg/kg body weight. (C) The same patient treated with daily dosage of 100 μg/kg body weight.

of neuroleptics in cortical and/or limbic areas (*14,17,18*). This is the only receptor for which all classes of neuroleptics have affinity in vitro (*17,18*). In contrast to classic antipsychotics, clozapine has a higher affinity for the recently cloned dopamine receptor subtypes D_3, D_4 and D_5 (*19–21*), presumably located in limbic and cortical areas, than for D_2 binding sites. It also binds with high affinity to D_1 as well as 5-HT_2 and 5-HT_3 serotonin receptors (*22,23*). Therefore, a complex interaction of clozapine with these receptor classes may be responsible for the neuroleptic effect. Moreover, the locations of these receptors in limbic and cortical areas agree with the low prevalence of extrapyramidal side effects mediated by nigrostriatal neurons. For typical high-potency neuroleptics, such as haloperidol, a dose-dependent occupation of striatal D_2 binding sites was reported in other studies using PET (*24*) and IBZM SPECT (*5*). The findings of our previous study confirmed these results in a larger patient group (*6*). Our findings are consistent with those of a study using ^{18}F-methylspiperone (*25*), which reported a 40% occupancy of striatal D_2 receptors in subjects taking low doses of haloperidol. It can be concluded that relatively low doses occupy a high proportion of D_2 receptors, as reflected by the steep decline of the curve in patients treated with haloperidol (*5,6,14,24*).

Risperidone is a recently licensed neuroleptic that was introduced to induce fewer EPS than typical neuroleptics such as haloperidol. However, in vitro binding studies of risperidone suggest a high affinity for D_2 receptors and potent 5-HT_2-blocking properties (*26,27*). In a PET study using ^{11}C-raclopride, 50% occupancy of striatal D_2 receptors was reported in volunteers receiving 1 mg of risperidone (*28*).

Although using ^{123}I-IBZM SPECT to investigate dopamine D_2 occupancy does not provide absolute quantitative measures of tracer binding to dopamine D_2 receptors, as is possible with PET, this method has proven to be valid and reproducible in assessing D_2 occupancy in normal volunteers, drug-naive patients with schizophrenia and patients receiving different classes of neuroleptics (*6,15,29,30*). Furthermore, PET studies using semiquantitative approaches and relative measures have been shown to reflect the results obtained with absolute quantification (*28*). Our results clearly indicate that ^{123}I-IBZM SPECT can distinguish between groups of patients taking typical neuroleptics and neuroleptic-free patients. Thus, the occupancy of central dopamine receptors, which is thought to be the essential pharmacological mechanism in the action of neuroleptics (*29*), can be visualized with IBZM SPECT imaging.

The moderate degree of receptor occupancy with low doses of risperidone predicts that high levels of D_2 receptor occupancy should be found at clinical doses. In a study of five patients treated with daily doses up to 12 mg (*31*), mean (S − BG)/BG ratios of 0.23 (normal value in this study is 0.68) were found. Indeed, our study confirmed that patients with the highest daily doses of risperidone (8 mg) presented with the lowest ratios. These results suggest high levels of dopamine D_2 receptor occupancy with risperidone, indistinguishable from the patterns found in patients taking low dosages of typical neuroleptics and significantly higher than those in clozapine-treated patients. However, when comparing the dose-response relationship, the curve of risperidone fits between the curve of haloperidol, with its steep decline, and the curve of clozapine. For the haloperidol and risperidone data, the monoexponential fitting gives the most appropriate plausible correlation coefficient. The rather low occupancy of dopamine D_2 receptors by clozapine fits to a linear as well as to a monoexponential model. However, the exponential fit gives the strongest correlation fitting, and from the biological point of view, a linear regression model seems very unlikely to explain a dose-dependent receptor occupancy, as this model would result in a specific binding of less than 0 at sufficiently high dosages. Previous in vivo functional imaging studies assessing the D_2 occupancy of risperidone have consisted of reports of either single patients or normal subjects not always receiving clinically relevant drug regimens (*28,31*). Our study investigated the in vivo behavior of risperidone with respect to the D_2 occupancy and the incidence of EPS.

Some patients received concomitant medication. According to the literature, there is no evidence for possible influence of these drugs on the binding of IBZM to the dopamine D_2 receptor (*32*). Two of these belong to the group of antidepressants known as tricyclic psychotherapeutic agents. The mechanism of these drugs is not definitely known. They are not central nervous system stimulants or monoamine oxidase inhibitors. The current hypothesis is that the clinical effects are due to the influence on the reuptake of norepinephrine. The other drug that has been occasionally applied is diazepam. Its influence on the dopaminergic system has not been described. However, none of our patients received medication on the day before or the day of the IBZM examination.

The characterization of high levels of D_2 occupancy in vivo are in clear contrast with the low incidence of EPS reported in recent clinical trials with this drug (*31,33*). In our patient group, EPS were found in 40% of the patients, which is less than the percentage obtained using haloperidol. These findings are in line with results reported in the literature (*34*). The mechanisms responsible for the low incidence of EPS are still unclear. In studies of typical neuroleptics such as haloperidol, it has been shown that EPS are related to the level of dopamine D_2 receptor occupancy (*5,6,16*). However, as previously described, the relationship between dopamine D_2 receptor occupancy and EPS is complex, which may account for the fact that very high doses of haloperidol (10 times higher than those used in our study) may in some cases not produce EPS (*35*). Contrary to typical neuroleptics, new generation neuroleptics such as risperidone showed an additional, even higher affinity to 5-HT_2 receptors than that to dopamine D_2 receptors (*36*). This property is similar to the 5-HT_2 affinity of atypical neuroleptics such as clozapine; however, the D_2 receptor affinity of clozapine is much less. In the case of risperidone, the crucial factor preventing the development of significant EPS may indeed be the high 5-HT_2-blocking potency of the drug (*10*). It has been suggested that concomitant blocking of 5-HT_2 receptors may exert a protective effect against EPS induced by D_2 antagonism (*8,26*). The reported 5-HT_2 versus D_2 potency ratio is about 20 (*37*). The combination of both receptor occupancies and the overblockade of 5-HT_2 receptors compared to D_2 receptors is believed to reduce the incidence of EPS in patients treated with risperidone. Consistent with the findings of our study, the in vivo and in vitro dopamine D_2 receptor occupancy of risperidone reported by Schotte et al. (*37*) was closer to that of typical neuroleptics (haloperidol) and higher than that of clozapine. This would suggest that the EPS benefits of risperdone cannot be explained by low D_2 binding, but may indeed be related to its high 5-HT_2 affinity. However, the emergence of EPS at higher levels of D_2 receptor occupancy in this study and in other publications (*28,34*) would suggest that risperidone's high 5-HT_2 affinity provides only a relative protection from EPS. The findings suggest that high levels of D_2 receptor occupancy do not necessarily induce EPS and therefore do not prevent a neuroleptic drug from being classified as atypical (*31*).

CONCLUSION

Our findings suggest an exponential relationship between striatal D_2 receptor occupancy and the total daily dose of risperidone in a larger number of patients using a wide range of dosages. We clearly showed that risperidone, which was thought not to occupy dopamine D_2 receptors to a large extent, inhibits IBZM binding more than expected. However, even patients presenting with a receptor occupancy above a threshold of 53% were EPS free. A relationship between the presence of EPS and the individual dosage was not verified. Compared to our previous studies of the typical neuroleptic haloperidol and the atypical neuroleptic clozapine, the dose-response curve of dopamine D_2 receptor binding during treatment with risperidone showed a closer similarity to the curve of haloperidol.

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