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What is This?

Striatal dopamine D_2 receptor binding of risperidone in schizophrenic patients as assessed by ^{123}I-iodobenzamide SPECT: a comparative study with olanzapine

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The aim of this investigation was to compare the degree of striatal dopamine-(D_2) receptor blockade by two atypical antipsychotic drugs, risperidone and olanzapine. The percentage of D_2 receptor occupancy during treatment was calculated by comparing the results of ^{123}I-iodobenzamide SPECT with those from healthy control subjects. Twenty inpatients suffering from schizophrenia or schizoaffective psychosis according to DSM IV/ICD-10 criteria were treated with clinically recommended doses of risperidone and compared with 13 inpatients treated with up to 20 mg olanzapine. Neuroleptic dose and D_2 receptor blockade correlated strongly for both risperidone (Pearson $r = –0.86$, $p = 0.0001$) and olanzapine (Pearson $r = –0.77$, $p = 0.002$). There was no significant difference between the D_2 receptor occupancy of the two substances when given in the clinically recommended dose range (unpaired t-test, $t = –0.112$, $p = 0.911$).

Key words: atypical neuroleptics, dopamine D_2 receptor, ^{123}I IBZM, olanzapine, risperidone, SPECT

Introduction

The antipsychotic action of typical neuroleptics (i.e. reduction of positive symptoms such as hallucinations, and psychotic and paranoid perception of subjective reality) is associated with the ability of these drugs to block the striatal dopamine (D_2) receptor. Under treatment with typical neuroleptics, at least 5–30% of patients develop severe side-effects, namely extrapyramidal symptoms (EPS), which contribute to noncompliance rates approaching 50% (Kane, 1987; Tollefson and Sanger, 1997).

Clozapine was the first atypical neuroleptic and preceded the introduction of a group of neuroleptics characterized not only by dopamine D_2 receptor, but also 5-HT_{2A} receptor antagonism. A ten-fold higher affinity for 5-HT_{2A} receptors than for D_2 receptors has been proposed as the key property of the 'atypicals' (Meltzer et al., 1989). Substances fulfilling this criterion demonstrated a very low tendency to induce EPS and tardive dyskinesia (Kapur et al., 1997, Kapur, 1998; Kapur et al., 1998).

Further atypical neuroleptics introduced over the last few years (e.g. risperidone, olanzapine, sertindole, ziprasidone and quetipine) are still under experimental and clinical investigation and their receptor profiles have been established in vitro and in vivo (Gerlach and Peacock, 1995; Bymaster et al., 1996; Richelson, 1996; Schotte et al., 1996).

Beside clozapine, risperidone and olanzapine are the most frequently clinically used substances of this group. For risperidone and its active metabolite 9-OH-risperidone, an eight- and 17-fold lower affinity for the D_2 receptor, respectively, with slightly less affinity for D_3 compared to haloperidol, was shown in vivo in rats (Schotte et al., 1996). Both compounds exhibited the highest affinity for the 5-HT_{2A} receptor and the least affinity for the D_2 receptor (potency ratios 19 and 22, respectively). Olanzapine (2-methyl-4-(4-methyl)-1-piperazinyl)-1OH-thieno[2,3-b][1,5]benzodiazepine) reveals a pharmacological profile similar to that of clozapine. Nevertheless, preclinical studies have demonstrated that the D_2 receptor affinity of olanzapine is higher than that of clozapine (Bymaster et al., 1996). Comparison studies between risperidone and olanzapine in rats have revealed lower affinity constants (K_i) of risperidone for the dopaminergic D_1 and histaminergic (H_1) receptors, and of olanzapine for the dopaminergic D_2 and D_3, serotonergic receptors, apart from 5-HT_{2C} and adrenergic α_1 and α_2 receptors (Bymaster et al., 1996; Schotte et al., 1996). In Table 1, the K_i values of both substances, compared to haloperidol, are listed according to the data of Schotte et al., 1996.

Clinical trials have defined efficacy and optimum doses for both risperidone and olanzapine (Marder and Meibach, 1995; Peuskens, 1995; Beasley et al., 1996). Risperidone has been found to be superior to haloperidol with respect to efficacy and safety (Peuskens, 1995); until recently, the recommended daily dose for risperidone was up to 8 mg (Peuskens, 1995; Möller et al., 1997) while clinical dose recommendations for olanzapine treatment are up to 20 mg/day (Tollefson et al., 1997; Tran et al., 1997b).

The mode of action of both substances in humans is still under investigation. It should be noted that the results of receptor occupancy from in-vitro or in-vivo animal experiments cannot be

Table 1 K_i values of risperidone, olanzapine and haloperidol from in-vitro binding studies in animal brain (Schotte, 1996)

Receptor	Species	Risperidone	Olanzapine	Haloperidol
D$_1$	Rat	620	250	270
D$_2$	Rat	3.3	17	1.4
D$_3$	Cloned rat	13	54	21
5-HT$_{1A}$	Rat	250	–	3080
5-HT$_{1B}$	Rat	2720	2850	> 5000
5-HT$_{2A}$	Rat	0.16	1.9	25
5-HT$_{2C}$	Pig	63	7.1	> 5000
5-HT$_3$	Mouse	> 5000	84	> 5000
5-HT$_6$	Cloned rat	420	2.5	> 5000
5-HT$_7$	Cloned mouse	1.6	120	380
α_1	Rat	2.3	60	19
α_2	Rat	7.5	–	> 5000
H$_1$	Guinea-pig	2.6	3.5	730

assumed to indicate the binding of a drug in humans (Arndt *et al*., 1997). For example, a difference between the striatal dopamine D$_2$ receptor occupancy rate in animals and humans was demonstrated for the neuroleptic remoxipride (Busatto *et al*., 1995). Therefore, there is a need to study the receptor profile of new antipsychotic substances *in vivo* in humans. Nuclear medicine imaging techniques such as ^{123}I-iodobenzamide (IBZM)-SPECT and ^{11}C-raclopride- or ^{14}N-methylspiperone-PET are potentially suitable methods for this purpose.

For risperidone, SPECT and PET data on the degree of dopamine D$_2$ receptor occupancy in humans are available. Data show that risperidone given in different dose regimes occupies the striatal dopamine D$_2$ receptor at a level close to that of haloperidol (Kerwin *et al*., 1993; Busatto *et al*., 1995; Farde *et al*., 1995; Küfferle *et al*., 1996).

In a number of PET and SPECT studies, there are conflicting findings regarding the striatal D$_2$ receptor occupancy with olanzapine. Higher D$_2$ occupancy has been demonstrated with SPECT (Kasper *et al*., 1998; Tauscher *et al*., 1999; Meisenzahl *et al*., 2000) and PET (Nyberg *et al*., 1997; Kapur *et al*., 1998b), but a lower D$_2$ occupancy rate, similar to that of clozapine, has been reported with SPECT (Pilowsky *et al*., 1996). Interestingly, a recent prospective double-blind SPECT study with 10 mg olanzapine reported a mean striatal D$_2$ occupancy of 49% (Bernardo *et al*., 2001). Kapur analysed D$_2$ receptor occupancy with PET and compared treatment groups in multiple-dose, steady-state regimens. By fitting, it was demonstrated that risperidone given in a daily dose of 5 mg has a binding level equal to that of olanzapine 20 mg/day (Kapur *et al*., 1999).

The aim of the present SPECT investigation was to compare the amount of striatal dopamine D$_2$ receptor blockade of risperidone and olanzapine in schizophrenic patients. Different doses of the drugs were used; the dose range was chosen according to the clinical needs but was within the clinically recommended range. This means that no prospectively fixed doses were given, but none of the patients was treated with higher or lower doses than defined in phase three clinical trials (Peuskens, 1995; Möller *et al*., 1997; Tollefson *et al*., 1997; Tran *et al*., 1997b).

Methods

Subjects

Consecutively admitted inpatients with a diagnosis of schizophrenia or a schizoaffective illness according to DSM-IV/ICD-10 criteria were included in the study. Eight males and 12 females were treated with risperidone and eight males and five females with olanzapine. The mean (± SD) age was 39.2 (± 13.26) years (range 19–68 years) for the risperidone and 35.0 (± 12.8) years (range 22–63 years) for the olanzapine group. Groups were comparable with respect to age (unpaired *t*-test, $t = 0.906$, $p = 0.372$) and gender (unpaired *t*-test, $t = -1.199$, $p = 0.239$).

According to DSM IV/ICD-10 criteria, 13 patients were diagnosed as paranoid, three as disorganized and four as schizoaffectively ill in the risperidone group, while there were six paranoid, five disorganized and two schizoaffective patients in the olanzapine group.

For patients pretreated with oral neuroleptics (12 patients in the risperidone and 10 patients in the olanzapine group), a 3-day washout period preceded commencement of the study medication. The dependency of receptor blockade on the dose per mg/kg body weight was analysed. Before the SPECT scan was performed, patients had been treated for 1–33 (mean ± SD, 8.8 ± 7.59) weeks with risperidone at a daily dose of 2–8 mg per day (mean 4.85 ± 2.28 mg); mg/kg body weight 0.03–0.13 (mean ± SD, 0.07 ± 0.03). Olanzapine was administered at a daily dose of 5–20 mg per day (mean ± SD, 11.9 ± 12.8); mg/kg body weight 0.05–0.28 (mean ± SD, 0.16 ± 0.07) for a minimum of 2 to a maximum of 8 (mean ± SD, 3.7 ± 1.6) weeks (Table 2). None of the patients were receiving any other neuroleptic substance at the time of the SPECT. Patients having been treated with depot formulation 3 months before the study entrance were excluded. Concomitant medication was restricted to biperiden in both groups. However, in the risperidone group, one patient received doxepine, another amitryptiline, and one occasionally benzodiazepines.

Ethical approval for the SPECT investigation was provided by the local ethics committee and the study was performed in accordance with the ethical standards defined in the Declaration of Helsinki 1975, revised Hong Kong 1989. All patients gave their informed consent to participate in the study.

SPECT investigation

In both treatment groups, ^{123}I-IBZM-SPECT was performed using identical protocols. SPECT scanning was typically performed 14 h after the last dose of antipsychotic medication (i.e. the last medication was given on ward at the evening before the day of scintigraphy). ^{123}I-IBZM was chosen as a highly selective radiotracer for striatal D$_2$ receptors. All patients were administered

Table 2 Characteristics of the risperidone group

Risperidone treated patients	Gender (M/F)	Age (years)	DSM IV/ICD-10 diagnosis	Dose (mg/kg body weight)	Total dose per day (mg)	Duration of treatment (weeks)
1	F	56	16 schizophrenic	0.029	2	1
2	M	29	4 schizoaffective	0.029	2	3
3	M	32		0.037	3	3
4	F	63		0.039	2	10
5	M	42		0.041	3	9
6	F	38		0.041	3	6
7	F	33		0.041	3	33
8	F	25		0.042	3	12
9	F	62		0.053	4	8
10	M	47		0.058	4	1
11	M	36		0.059	4	15
12	M	20		0.067	6	6
13	M	35		0.075	6	8
14	F	24		0.093	8	8
15	F	47		0.100	8	22
16	F	36		0.100	6	6
17	F	24		0.100	8	9
18	F	56		0.100	8	1
19	M	35		0.120	8	6
20	F	38		0.128	6	8
Mean ± SD		39.15 ± 13.24		0.068 ± 0.32	4.85 ± 2.28	8.75 ± 7.59

Risperidone treated patients	[STR – BKG]/BKG	D_2-occupancy rate (%)	Comedication
1	0.60	32	
2	0.62	37	
3	0.60	37	Benzodiazepines (occasionally)
4	0.30	69	
5	0.60	37	
6	0.40	43	
7	0.39	59	Amitryptiline
8	0.40	59	
9	0.40	59	
10	0.39	57	
11	0.40	59	
12	0.50	44	Doxepine
13	0.40	58	
14	0.20	79	
15	0.30	69	
16	0.07	78	
17	0.27	91	
18	0.20	72	(All patients:
19	0.20	78	biperiden if
20	0.32	65	necessary)
Mean ± SD	0.38 ± 0.15	59.1 ± 16.6	

185 MBq (5 mCi) of ^{123}I-IBZM intravenously as a bolus injection. SPECT scans were acquired using a triple-headed gamma camera equipped with high resolution fan-beam collimators (Prism 3000 XP, Picker Intl., Cleveland, OH, USA). The acquisition parameters included a 20% energy window centred on 159 keV, a rotational radius of 13 cm or less, 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 s per projection). Reconstruction of projection images was performed by filtered back-projection followed by filtering with a low pass filter. Chang's first order method was used for uniform attenuation correction. Uniform image reslicing was performed by drawing a line connecting the anterior-most aspect of the frontal pole to the posterior-most aspect of the occipital pole. This procedure approximates the line connecting the anterior and posterior commisures (AC–PC line). To assess specific tracer uptake in the striatum, the region of interest (ROI) technique was used. Mean specific activity in basal ganglia regions was calculated by subtracting the mean counts per pixel in the background (BKG) from the mean counts per pixel in the basal ganglia region, and dividing the result by the mean counts per pixel in the background [(STR – BKG)/BKG]. Templates were used to define striatal ROIs. The size and shape of the templates was established and optimized using the data from a control group, as previously described (Dresel *et al*., 1998). The predefined templates were adjusted to fit individuals so that only minor corrections according to the individual shape and size were necessary. By performing this procedure, intraobserver reliability

was enhanced. The operator was blind to clinical data. D$_2$ receptor occupancy of the healthy controls registered by ^{123}I-IBZM-SPECT was considered to be normal. No morphological fusion with magnetic resonance imaging images was used. The non-specific background activity was estimated by drawing a 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 activity of the two slices.

^{123}I-IBZM binding in the patients was compared to an age-matched control group and to patients treated with olanzapine. Patient data were expressed as a percentage of normal binding with a 100% value of [(STR – BKG)/BKG] = 0.95 for both the risperidone and the olanzapine group.
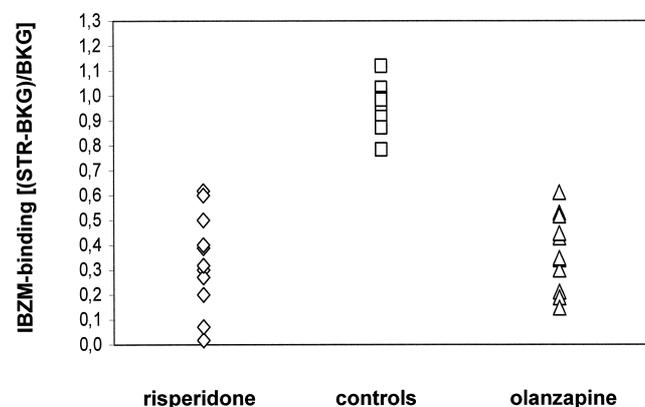
Measurements in controls were used to assure that this approach resulted in comparable data. The control group consisted of 10 healthy, age- and sex-matched subjects. There was no significant difference between patients and healthy controls with respect to age and gender.
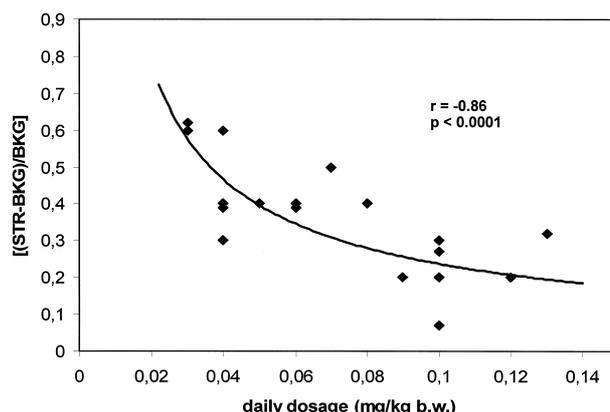
Statistical analysis

For statistical analysis of SPECT, clinical and risperidone group data, a one-way analysis of variance (ANOVA) was performed with post-hoc tests (Scheffé) to test the significance of differences. Student's *t*-test was performed to compare two independent groups (i.e. risperidone versus the control group, risperidone versus the olanzapine treatment group, low versus high risperidone group). Mono-exponential fitting was applied to all data. Equality of variances were tested using Levine's test of equality of variances. Continuous values were correlated where necessary using Pearson correlation coefficients or Spearman's rho. $p < 0.05$ was considered statistically significant.

Results

Patients treated with risperidone showed a markedly reduced dopamine D$_2$ receptor binding of IBZM compared to healthy controls, as did olanzapine-treated patients (Fig. 1). Striatal IBZM binding in the risperidone-treated patients, expressed as [(STR-BKG)]/BKG, was in the range 0.07–0.62 (mean 0.38 ± 0.15),

Figure 2 dose-response relationship of IBZM-binding and daily dosage in mg/kg body weight of risperidone (n = 20)
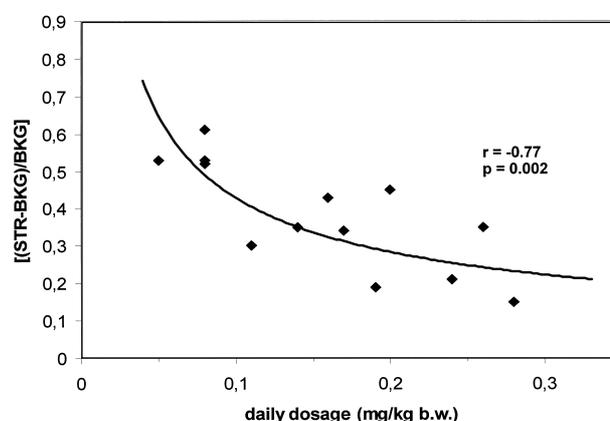
Figure 3 dose-response relationship of IBZM-binding and daily dosage in mg/kg body weight of olanzapine (n = 13)

which is significantly lower than in the control group (mean 0.95 ± 0.10), as shown by statistical analysis (ANOVA: $F = 115.53$, $p = 0.0001$). The striatal D$_2$ receptor occupancy rate induced by risperidone treatment was 59.1 ± 16.6%, ranging individually between 32% and 91%. The degree of the occupancy of the dopamine D$_2$ receptors presented an exponential dose–response relationship (Pearson $r = –0.86$, $p = 0.0001$) (Fig. 2). Patients' daily dose, duration of treatment, IBZM-binding behaviour and D$_2$ occupancy rate are shown in Table 2.

Comedication did not seem to play an important role in our patient group. One patient was treated with amitryptiline, another with doxepine and a third occasionally with diazepam. Diazepam had last been administered 1 week before the SPECT scan was performed. D$_2$ receptor occupancy rate of the amitryptiline-treated patient was the same as in three patients who were not comedicated and who received comparable or even higher doses of risperidone. The doxepine-treated patient also had an IBZM-binding in the range of variance, as did the patient who occasionally took benzodiazepines (Table 2).

Comparison of the risperidone-treated with the olanzapine-treated group revealed no significant differences with respect to the striatal D$_2$ receptor binding of IBZM (unpaired *t*-test, $t = –0.066$, $p = 0.947$) or D$_2$ receptor occupancy rate (unpaired *t*-test,

Figure 1 IBZM-binding of risperidone and olanzapine treated patients compared to healthy controls

$t = -0.112$, $p = 0.911$) induced by the two substances. The only significant difference found concerned the duration of treatment: the risperidone-treated patients had a significant longer treatment duration with the substance (mean 8.8 versus 3.7 weeks; unpaired t-test, $t = -4.608$, $p = 0.0001$).

The effect of duration of medication with respect to striatal binding of IBZM was therefore tested seperately in the risperidone and olanzapine groups. There was no correlation between duration of medication and striatal binding of IBZM for either risperidone (Spearmans' rho = –0.144) or olanzapine (Spearmans' rho = 0.475).

Discussion

The aim of our study, using SPECT, was to assess *in vivo* the degree of striatal dopamine D_2 receptor occupancy of risperidone in schizophrenic patients compared to that of olanzapine. The risperidone group included 20 patients, which to our knowledge is the largest sample investigated to date.

Our investigation revealed that risperidone treatment led to a significant, dose-dependent dopamine D_2 receptor occupancy rate. The hypothesis of a strong correlation between dose in mg/kg body weight with striatal D_2 receptor blocking, as hypothesized (Tauscher *et al*., 1999) and confirmed (Meisenzahl *et al*., 2000) for olanzapine, was therefore also confirmed for risperidone.

Testing the D_2 occupancy rate of different neuroleptics in one laboratory minimizes methodological influences. We compared our risperidone data with the binding characteristics of a group of olanzapine-treated patients who were highly comparable with respect to sociodemographical characteristics. Olanzapine binding to the striatal dopaminergic D_2 receptors was proposed to be similar to that of clozapine (Pilowsky *et al*., 1996). Tauscher reported a higher blocking ability by olanzapine compared to clozapine (Tauscher *et al*., 1999). In a recently published study on olanzapine administered at higher doses than 20 mg per day, receptor occupancy rate was still more pronounced (Meisenzahl *et al*., 2000). Our data suggest that, in age- and sex-matched patients, there is no difference in the dopamine D_2 receptor blockade by risperidone and olanzapine when these are given in the clinically recommended dose range. Both substances show D_2-binding curves different to clozapine and more closely related to haloperidol, although without the same steep decline.

In line with our findings, Lavalaye *et al*. (1999) found no differences in the mean binding rates between both groups when investigating the D_2 occupancy by ^{123}I-IBZM-SPECT in 13 patients treated with risperidone (daily dose mean 4.2 mg, range 2–8 mg) and 23 patients treated with olanzapine (daily dose mean 15.4 mg, range 5–30 mg) (Lavalaye *et al*., 1999). However, by subdividing patients into subgroups of the most prescribed doses, with eight patients receiving 4 mg risperidone per day, and nine patients 15 mg olanzapine, a significantly lower occupancy rate for the olanzapine group was detected.

Lavalaye *et al*. reported a mean occupancy rate of 76% in the 13 patients receiving 2–8 mg risperidone (mean dose 4.2 mg/day). Our group, consisting of 20 patients with a 0.5 mg higher mean dose (4.9 mg/day), shows a lower occupancy rate (59.1%). Some methodological limitations might hinder a direct comparison. Lavalaye *et al*. performed SPECT imaging after at least 6 weeks of steady-state treatment of atypical medication with risperidone, whereas duration of treatment in our risperidone-treated patient group included a time period of 1–33 weeks. Additionally, Lavalaye *et al*. used different SPECT data processing, including a different background region (occipital lobe versus the frontal lobe in our study). Nevertheless, while the degree of occupancy of the dopamine D_2 receptors in our group presented an exponential dose–response relationship, Lavalaye *et al*. were unable to detect a relationship between the dose of risperidone and D_2 receptor occupancy.

In a SPECT investigation of 11 patients under treatment with risperidone, Küfferle *et al*. (1996) reported rates of 63.8% D_2 occupancy in a predefined low dose patient group (3 mg each, five patients) versus 74.3% D_2 occupancy in the high dose group (8 mg each, six patients) (Küfferle *et al*., 1996). To enable direct comparison with this study, we defined a low dose group with 11 patients receiving up to 4 mg risperidone (mean 3.1 mg/day) and a high dose group with nine patients receiving a daily dose of between 6 and 8 mg (mean 7.1 mg/day). These subgroups revealed significantly different D_2 occupancy rates (49.8% and 71.2%, respectively). Therefore, especially the D_2 occupancy in our high dose range may support the findings of Küfferle *et al*.

A case report in a patient treated with 12 mg risperidone a day presented a D_2-SPECT-binding comparable to typical neuroleptics (Kerwin *et al*., 1993). The group repeated their findings in six patients who were being treated with risperidone at a dose of 4–12 mg daily (Busatto *et al*., 1995). It should be noted that the dose range used equals the one formerly recommended for risperidone. The data of Busatto *et al*. (1995) are difficult to compare with ours in detail because they are given as binding rates in the left versus right striatum separately. Percent binding values of risperidone are not listed.

To date, all SPECT studies that have investigated D_2 occupancy of risperidone examined subgroups of dose ranges or were unable to provide an exponential dose–response relationship between dose of risperidone and D_2 receptor occupancy.

Kapur *et al*. (1999) presented a ^{11}C-raclopride-PET study comparing D_2- (and 5-HT$_{2A}$-) receptor blockade under multiple-dose, steady-state regimens with risperidone ($n = 16$, mean dose 5.01 mg/day), olanzapine ($n = 17$, mean dose 18.8 mg/day) and clozapine ($n = 11$, mean dose 425.0 mg/day). Again in line with our findings, they show that, in a comparable number of patients, there is no difference in the D_2-binding of ^{11}C-raclopride in the risperidone versus olanzapine group. Kapur fitted the 5 mg dose of risperidone to the 20 mg dose of olanzapine as equipotent in D_2 occupancy rate (Kapur *et al*., 1999). Although this equipotency of both doses cannot be provided by our data, it should be noted that PET and SPECT data are difficult to compare because of the broad range of methodological differences between these techniques. Generally, another confounding variable in those studies is the difference in time interval between last medication intake and SPECT scanning.

Our study is not without limitations. In our risperidone-treated group, three patients were treated for only 1 week. However, the percentage D_2 occupancy did not differ from the mean value of the whole group when only those patients with a minimum treatment of 2 weeks were considered. Additionally, a clear correlation between daily dose of risperidone and the degree of D_2 receptor binding compared to olanzapine was demonstrated. We could not

collect plasma levels at the time of SPECT investigations, but the relatively high D$_2$ receptor occupancy made us confident that the compliance of our inpatients was good. Furthermore, patients were not randomly assigned in a prospective fashion to take fixed-multiple dose regimes for clinically relevant doses of risperidone and olanzapine. Additionally, we cannot provide standardized data on clinical symptoms or EPS in our patient groups.

Problems of nuclear medicine imaging technique data from SPECT or PET, with respect to comparing D$_2$ receptor occupancy, clinical efficacy and side-effects in different treatment regimes, have only recently become apparent. From a methodological viewpoint, the real benefit of novel antipsychotics in comparison to each other and with respect to classical antipsychotics may be obscured in drug trials with non-equipotent dosing (Nyberg and Farde, 2000). A first remarkable PET study in this field was performed in order to evaluate the minimal effective dose of risperidone by fixed different and subsequently administered doses in a sample of schizophrenic patients (Nyberg *et al.*, 1999). By investigating the relationship between dose, plasma concentration and D$_2$ and 5-HT$_{2A}$ receptor occupancy of risperidone, guidelines for the minimal effective dosing of risperidone emerged. A relevant receptor occupancy of 70–80% with risperidone given at a daily dose of 4 mg with minimal risk of extrapyramidal side-effects was detected.

Atypical neuroleptics have been characterized by a minimally ten-fold higher affinity for 5-HT$_{2A}$ than for dopamine D$_2$ receptors. In combination with a threshold level of striatal D$_2$ receptor occupancy between 74% and 82%, this is regarded as the main protection against the severe side-effects, especially concerning EPS, of the classical neuroleptics (Meltzer *et al.*, 1989; Farde *et al.*, 1992). Risperidone and olanzapine exhibit this 5-HT$_{2A}$ versus D$_2$ receptor blocking capability, at least in animal experiments (Bymaster *et al.*, 1996; Schotte *et al.*, 1996). Despite its clozapine-like structure, olanzapine equals risperidone regarding an affinity for the cloned human D$_2$ receptor (Bymaster *et al.*, 1996; Schotte *et al.*, 1996). Clinical experience, on the other hand, nevertheless shows different EPS-inducing behaviour of both substances: patients treated with risperidone develop EPS more often than those treated with olanzapine (Bymaster *et al.*, 1996; Tran *et al.*, 1997a; Leucht *et al.*, 1999; Remington and Kapur, 1999). Our data support the hypothesis that the clinically documented difference between risperidone and olanzapine for the incidence of EPS cannot be explained solely by blocking of the striatal D$_2$ receptor. Other components of the receptor binding profiles of both substances (i.e. binding to the 5-HT-system or the muscarinic receptors) may play an important role in this respect (Bymaster *et al.*, 1996; Schotte *et al.*, 1996).

Fast dissociation from the dopamine D$_2$ receptor caused by a low affinity at the D$_2$ receptor without reference to any other receptor profile is sufficient to produce atypical antipsychotic activity (Seeman and Tallerico, 1999; Kapur and Seeman 2001). It was suggested that antipsychotic drugs with *k*-values > 2 nmol/l (e.g. olanzapine and clozapine) elicit low levels of parkinsonism because they bind more loosely than dopamine itself at the D$_2$ receptor (Seeman and Tallerico, 1998, 1999). Finally, comparative studies using different radioligands also need to reflect the potential variable displacement of the antipsychotic drug due to higher or lower affinity of the competing radioligand (Seeman and Van Tol, 1995).

Recent data concerning another difference between risperidone and olanzapine (i.e. the different capability to block NMDA-antagonist-induced alterations of brain metabolism in the rat) (Duncan *et al.*, 2000) extend the field of discussion regarding this topic and certainly have to be further evaluated in this context. Olanzapine, but not risperidone, blocks ketamine-induced 2-DG uptake in different brain regions of the rat (Duncan *et al.*, 2000). The same difference was shown by this group for clozapine versus haloperidol. Further characteristics of risperidone and olanzapine therefore seem to be important, which somehow make risperidone more similar to haloperidol despite its more or less identical D$_2$ blocking properties, even *in vivo*. Interestingly, a higher dose of olanzapine was required to completely block the ketamine-effects than would be expected if the D$_2$ and 5-HT$_2$ receptor blocking properties of olanzapine were solely responsible for its action. These data may support the importance of analysis of the schizophrenic illness as a combined glutamatergic-dopaminergic, or cortico-striato-thalamico-cortical feedback disorder (Weinberger, 1987).

In conclusion, using SPECT, we demonstrated *in vivo* the degree of striatal dopamine D$_2$ receptor binding in a large sample of 20 patients with schizophrenia, who were being treated with risperidone, and compared these data with the degree of striatal dopamine D$_2$ receptor binding of olanzapine. Our study demonstrated an exponential dose–response relationship in 20 patients treated with 2–8 mg of risperidone daily. Comparison of the risperidone-treated group with the olanzapine-treated group revealed no significant difference with respect to striatal D$_2$ receptor binding of IBZM or the D$_2$ receptor occupancy rate induced by the two substances. Our results indicate that the dose–response relationship of risperidone is similar and closer to that of haloperidol than to that of clozapine. Risperdone occupies a considerable percentage of D$_2$ receptors *in vivo* in a large range of clinically relevant doses.

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