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Dopamine D_2 receptor occupancy by olanzapine or risperidone in young patients with schizophrenia

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Abstract

A crucial characteristic of antipsychotic medication is the occupancy of the dopamine (DA) D_2 receptor. We assessed striatal DA D_2 receptor occupancy by olanzapine and risperidone in 36 young patients [31 males, 5 females; mean age 21.1 years (16–28)] with first episode schizophrenia, using [^{123}I]iodobenzamide (IBZM) SPECT. The occupancy of DA D_2 receptors was not significantly different between olanzapine and risperidone. However, in subgroups of most prescribed doses, DA D_2 occupancy was higher in the risperidone 4-mg group (79%) compared to the olanzapine 15-mg group (62%). [^{123}I]IBZM binding ratios decreased with olanzapine dose ($r = -0.551$; $P < 0.01$), indicating higher DA D_2 receptor occupancy with higher olanzapine dose. Akathisia and positive symptoms were correlated with [^{123}I]IBZM binding ratio ($r = -0.442$; $P < 0.01$; and $r = -0.360$; $P < 0.05$, respectively). Prolactin (PRL) levels were elevated in the risperidone, but not in the olanzapine group, at comparable D_2 receptor occupancy levels. In the olanzapine group, PRL levels were correlated with [^{123}I]IBZM binding ratio ($r = -0.551$; $P < 0.01$). In conclusion, both olanzapine and risperidone induce a high striatal D_2 receptor occupancy, dependent on dose and group formation. The lower incidence of prolactin elevation with olanzapine, compared to risperidone, may not be attributed to a lower D_2 receptor occupancy.

Keywords: Antipsychotic agents; Human; Brain; Single-photon emission-computed tomography; Benzamides; Prolactin

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1. Introduction

Schizophrenia is a severe and disabling psychiatric disorder with a heterogeneous symptomatology. Various theories have been developed to explain the pathophysiology of these various symptoms. The dopamine (DA) hypothesis (Carlsson, 1959) has generated strong arguments for the involvement of DA in the pathophysiology of psychotic symptoms. More recent studies refined this theory by stressing the enhanced sensitivity of the dopaminergic neurotransmission system (Lieberman et al., 1997). An enhanced responsiveness of the nigrostriatal dopaminergic pathway has been shown in vivo with a pharmacological stress model and SPECT (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998). The proposed major role for DA in the pathophysiology of schizophrenia underlines the importance of studying intensively the in vivo influence of different antipsychotic drugs (AP) on the dopaminergic neurotransmission system.

Olanzapine and risperidone have been introduced as atypical AP with a good effect on positive and negative symptoms of schizophrenia (Peuskens, 1995; Beasley et al., 1996). The main benefit of atypical AP is a relatively low incidence of extrapyramidal side effects (EPS) compared with classic AP (Borison et al., 1992; Tran et al., 1997). However, EPS have been observed in patients treated with risperidone or olanzapine in high dosages (Marder and Meibach, 1994; Kapur et al., 1998). Several studies have been performed to explain the low incidence of EPS by examining the striatal DA D_2 receptor occupancy by atypical AP. However, the results of these studies are not consistent in the percentage of striatal DA D_2 receptor occupancy by olanzapine (Pilowsky et al., 1996; Kapur et al., 1998; Nordström et al., 1998; Tauscher et al., 1999).

The aim of the present study was to evaluate the occupancy of striatal DA D_2 receptors by maintenance doses of olanzapine and risperidone, using iodine-123 iodobenzamide ($[^{123}I]$IBZM) SPECT in a large patient cohort. All patients were adolescents or young adults, administered AP after a first or second psychotic episode. The small age range in this group is an advantage over other studies because of the decrease of DA D_2 receptors with age (Volkow et al., 1998), which can be of influence on the total radioligand binding. $[^{123}I]$IBZM is a suitable SPECT radioligand for visualisation of striatal DA D_2 receptors in the human brain (Verhoeff et al., 1991b). Moreover, we studied the correlation between occupancy of DA D_2 receptors, clinical symptoms and prolactin levels.

2. Methods

2.1. Subjects

A consecutive series of 39 young patients with schizophrenia were initially included in this study. Excluded were patients with prominent or recent alcohol or drug dependency.

All patients were admitted to the Adolescent Clinic of the Academic Medical Centre and attended a special program for adolescents with a first psychotic episode. Clinical diagnosis was confirmed in 37 out of 39 patients after discharge. Two patients were excluded from the study because of a different diagnosis (mood disorder with psychotic features), and one was excluded because of discontinuation of medication therapy during the study. Analysis of SPECT data was performed on the resulting 36 patients with schizophrenia (31 males, five females) according to DSM IV (American Psychiatric Association, 1994), ranging in age from 16 to 28 (mean = 21.1) years. All patients gave their written informed consent. This study is part of an ongoing trial in which the clinical response to the two atypical AP, olanzapine (Zyprexa®) and risperidone (Risperdal®) is compared. The two drugs under study were randomly allocated to patients who used classic neuroleptic drugs at intake. However, patients who were responding well to either one of the two drugs under study at intake continued their original medication. Drug dosing was flexible, according to psychotic symptoms. Eventually 23 patients were treated with olanzapine [average dose of 15.4 mg (range 5–30 mg)], and 13 patients

were treated with risperidone [average dose 4.2 mg (range 2–8 mg)].

SPECT imaging was always performed after a stable dose period of at least 6 weeks of study medication to ensure stabilisation of psychotic symptoms. At the moment of imaging, co-medication was kept as low as clinically achievable. A few patients used selective serotonin re-uptake inhibitors (SSRI) ($n = 7$) or benzodiazepines ($n = 6$) in the week of SPECT imaging. Three patients (nos. 11, 12, and 35) received a depot AP more than 3 months before SPECT imaging. Last intake of AP was the evening before scintigraphy for most patients. This study was approved by the medical ethical committee of the Academic Medical Centre in Amsterdam.

2.2. [^{123}I]IBZM SPECT procedure

SPECT imaging was performed with a brain-dedicated SPECT multidetector system (SME 810, Strichman Medical Equipment Inc., USA), linked to a Macintosh II computer. The Strichman camera consists of 12 individual crystals, each equipped with a focussing collimator. The transaxial resolution of this camera is 7.6 mm full width half maximum (FWHM) of a line source in air, and the axial resolution is 13.5 mm FWHM. All subjects received potassium iodide orally to block thyroid uptake of free radioactive iodide. [^{123}I]IBZM (specific activity of > 185 MBq/nmol; radiochemical purity of $> 95\%$) was injected intravenously at an approximate dose of 110 MBq. ^{123}I labelling of IBZM was performed by Amersham Cygne (Technical University Eindhoven, The Netherlands). SPECT image acquisition was always performed at 2 h p.i. (Verhoeff et al., 1991a). Slices were acquired during 220-s periods from the orbitomeatal line to the vertex using an interslice distance of 5 mm. Attenuation correction and reconstruction of the images was performed as described earlier (Verhoeff et al., 1993).

2.3. Data processing

For analysis of striatal [^{123}I]IBZM binding, the ratio of striatal to non-specific binding was calculated by summing up two transversal slices, representing the most intense striatal binding. Analyses were performed by one observer (J.L.), blinded to clinical data. A standard region of interest (ROI) template (constructed according to a stereotactic atlas and including regions for striatum and occipital cortex) was placed bilaterally on the acquired image. The ratio of specific striatal binding was calculated by dividing the striatal binding by occipital binding. This method is used as a reliable measure for estimation of [^{123}I]IBZM binding (Verhoeff et al., 1993).

Data obtained in normal control subjects [average age 24 years (range 19–31), $n = 9$] were used to calculate the percentage of occupancy of AP in the striatum. [^{123}I]IBZM binding in control subjects was symmetrical in the striatum with an average binding ratio of 1.92 (S.D. = 0.08). Percentage of occupancy of AP in patients was calculated as $(\text{ratio str/occ} - 1)/(1.92 - 1) * (-100) + 100$, as described by Küfferle et al. (1996).

2.4. Clinical interviews

Psychotic symptoms were rated, in the same week of SPECT imaging, by one of the researchers (J.L.) using the Structured Clinical Interview for the Positive and Negative Syndrome Scale [SCI-PANSS (Kay et al., 1986)]. Depression was rated with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Extrapyramidal symptoms were rated with three different rating scales: the Barnes Akathisia rating scale (Barnes, 1989), the Simpson-Angus rating scale (SA) (Simpson and Angus, 1970), and the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1974). All tests were performed at the time of the PANSS interview. The rater of the tests was blind to the results of the SPECT imaging. The SA and the AIMS were rated in 15 patients.

2.5. Prolactin

Blood samples for prolactin levels were taken in 27 patients, between 10.00 and 12.00 h, at the time of injection of [^{123}I]IBZM. Samples were measured by fluoroimmunoassay. PRL elevation was defined as higher than 15 μg/l for men and

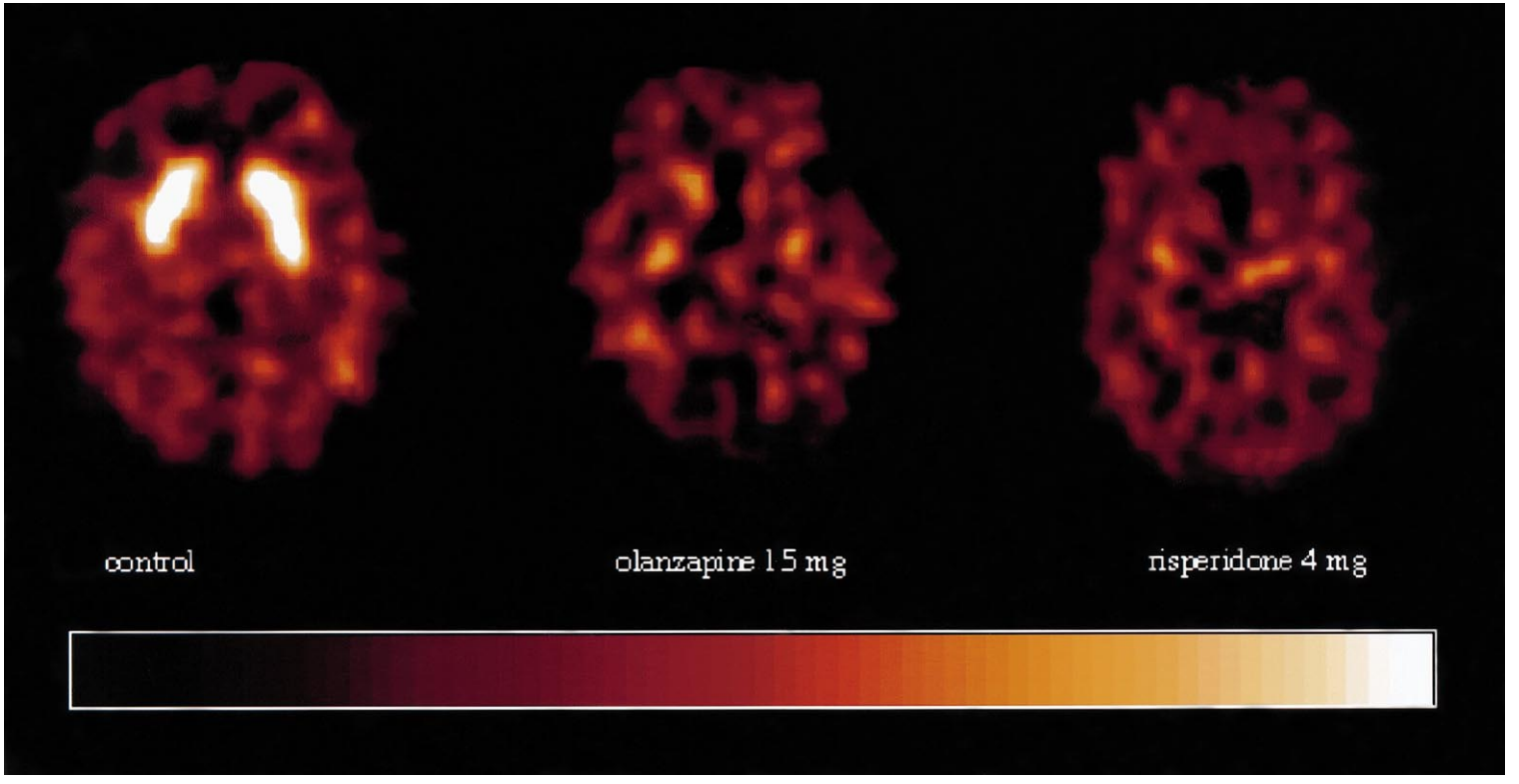

Fig. 1. [^{123}I]IBZM SPECT images of a healthy control and two schizophrenic patients treated with olanzapine (15 mg) and risperidone (4 mg). Transverse slices from the brain at the level of the striatum. The images of the patients clearly show much lower striatal binding of [^{123}I]IBZM than in the control subject. Levels of SPECT activity are colour encoded from low (black) to high (white).

higher than 22 μg/l for women. Thyroid function was screened at intake at the clinic and was normal in all subjects.

2.6. Statistics

Correlations were calculated using a one-tailed Spearman's rho non-parametric test. Analysis of variance (ANOVA) was used to compare the regional SPECT data in the patients and healthy control subjects. A Mann–Whitney *U*-test was used for comparison between two groups. Data analysis was carried out with statistical software (SPSS version 7.5).

Table 1
Demographic data and [^{123}I]IBZM binding ratios of 36 patients with schizophrenia[a]

Patient no.	Age (years)	Sex	Medication	Dose (mg/day)	Dose (mg/kg)	Co-medication
1	17	M	Olanzapine	5	0.100	
2	17	F	Olanzapine	5	0.077	
3	22	M	Olanzapine	10	0.133	Paroxetine 20 mg
4	19	M	Olanzapine	10	0.154	
5	20	F	Olanzapine	10	0.128	
6	25	M	Olanzapine	10	0.120	
7	27	M	Olanzapine	10	0.141	
8	20	M	Olanzapine	15	0.231	Oxazepam 30 mg
9	25	F	Olanzapine	15	0.188	Fluvoxamine 150 mg
10	22	M	Olanzapine	15	0.231	
11	19	M	Olanzapine	15	0.176	
12	23	M	Olanzapine	15	0.250	
13	16	F	Olanzapine	15	0.208	
14	20	M	Olanzapine	15	0.224	Paroxetine 30 mg
15	22	M	Olanzapine	15	0.163	Oxazepam 75 mg
16	20	M	Olanzapine	15	0.172	Oxazepam 10 mg
17	21	M	Olanzapine	20	0.267	
18	18	F	Olanzapine	20	0.408	Paroxetine 20 mg, alprazolam 1 mg
19	23	M	Olanzapine	20	0.222	Oxazepam 75 mg
20	21	M	Olanzapine	20	0.253	Paroxetine 20 mg
21	16	M	Olanzapine	20	0.263	
22	18	M	Olanzapine	30	0.300	
23	22	M	Olanzapine	30	0,242	Amitriptyline 200 mg
Mean				15.4	0.202	
(S.D.)				(6.4)	(0.074)	
24	19	M	Risperidone	2	0.027	
25	25	M	Risperidone	3	0.030	
26	22	M	Risperidone	3	0.038	
27	27	M	Risperidone	4	0.057	
28	17	M	Risperidone	4	0.044	Biperiden 2 mg, lithium 1000 mg
29	21	M	Risperidone	4	0.040	Biperiden 4 mg
30	19	M	Risperidone	4	0.075	Biperiden 2mg
31	28	M	Risperidone	4	0.066	Biperiden 2 mg
32	28	M	Risperidone	4	0.057	Biperiden 2 mg, fluoxetine 10 mg
33	17	M	Risperidone	4	0.054	
34	21	M	Risperidone	4	0.054	
35	24	M	Risperidone	6	0.073	Biperiden 2mg
36	18	M	Risperidone	8	0.100	Biperiden 2mg, clorazepate 50 mg
Mean				4.2	0.055	
(S.D.)				(1.5)	(0.020)	

Table 1 (*Continued*)

Patient no.	IBZM ratio	Occupancy (%)	PRL (μg/l)	Aka-thisia	PANSS Positive	PANSS Negative	PANSS General	MADRS
1	1.15	83.96		0	11	12	21	2
2	1.41	55.45	9.5	0	10	11	21	2
3	1.53	42.36		0	13	17	34	18
4	1.24	74.16	10	1	7	7	22	3
5	1.41	55.07	12.5	0	7	12	19	2
6	1.45	51.22	8.5	0	7	9	22	4
7	1.29	68.94	9.5	0	7	17	16	0
9	1.20	78.26		0	7	24	28	20
10	1.38	59.02	13	0	14	7	20	1
11	1.57	38.35	14.5	0	7	26	28	19
12	1.44	51.69	8.5	1	8	8	24	3
13	1.13	86.41	23[b]	0	9	11	18	9
14	1.40	57.03			10	13	33	
15	1.41	55.63	13	0	17	23	43	18
16	1.23	74.64	21[b]	2	9	13	22	6
17	1.24	73.91		0	9	15	25	11
18	1.10	89.65		3	20	22		25
19	1.28	69.57	10	2	7	17	25	5
20	1.15	84,02	19.5[b]	1	15	17	27	4
21	1.16	83.13	14	1		11	19	2
22	1.12	86.82		3	13	9	24	5
23	1.11	87.83	5	2	19	17	44	18
Mean	1.29	68			10.6	14.2	25.5	8.1
(S.D.)	(0.14)	(16)			(4.2)	(4.2)	(7.4)	(7.8)
24	1.29	68.94		0				2
25	1.20	77.74	26[b]	0	11	22	34	4
26	1.28	69.12	41[b]	0	8	15	20	7
27	1.07	92.91	39[b]	1	10	16	30	33
28	1.13	85.59	29[b]	3	9	12	20	4
29	1.36	60.98	48[b]	0	9	8	19	0
30	1.26	71.34	27[b]	2	14	15	31	5
31	1.21	77.70	23[b]	0	12	21	35	17
32	1.33	63.77	30[b]	1	9	19	35	17
33	1.02	98.02	42[b]	2	13	21	33	10
34	1.15	84.07	56[b]	0	10	9	17	4
35	1.40	56.93	51[b]	2	16	14	46	25
36	1.18	80.49	48[b]	1	14	16	29	10
Mean	1.22	76			11.3	15.7	29.1	10.6
(S.D.)	(0.11)	(12)			(2.5)	(4.6)	(8.6)	(9.8)

[a] IBZM ratio is striatum/occipital [^{123}I]IBZM binding.
[b] Elevated measure.

3. Results

3.1. [^{123}I]IBZM SPECT

Both patient groups showed a low striatal binding of [^{123}I]IBZM on visual inspection (Fig. 1). [^{123}I]IBZM binding in the striatum was symmetric (left/right ratio = 1.01), with no correlation of handedness for the patients, so average binding in left and right striatum was used for further analysis. Gender and age were not significantly correlated with [^{123}I]IBZM binding in either patient

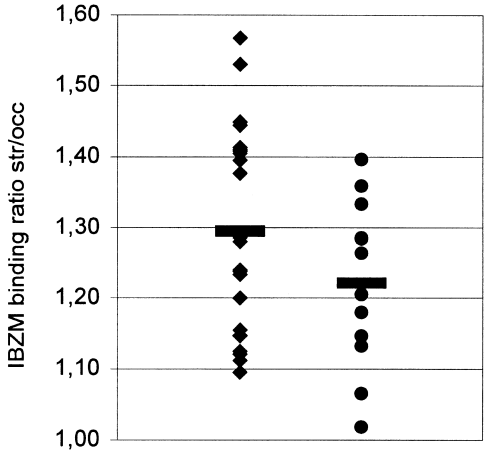

Fig. 2. Individual [^{123}I]IBZM binding ratios (striatum/occipital binding) in patients treated with olanzapine (♦) or risperidone (●).

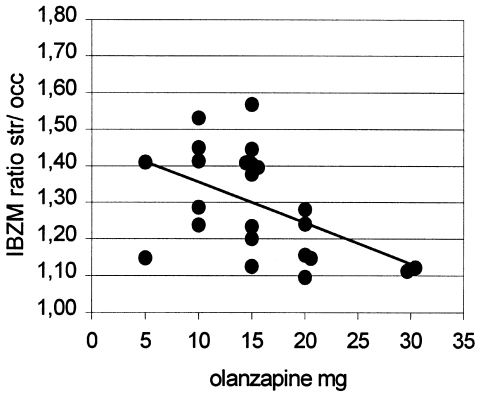

Fig. 3. Individual [^{123}I]IBZM binding ratios (striatum/occipital binding) in patients treated with different doses of olanzapine.

group. Ratios in the patient groups were significantly lower than in control subjects ($P < 0.01$; data not shown).

The ratios of striatal to non-specific [^{123}I]IBZM binding for olanzapine and risperidone are shown in Table 1 and Fig. 2. The occupancy of striatal DA D_2 receptors by olanzapine was not significantly different from that in patients treated with risperidone (Mann–Whitney $U = 107.0$; $P = 0.16$). To exclude a possible confounding effect of comedication, we also analysed our data restricted to patients without SSRI and benzodiazepines. In these subgroups, the mean binding ratio was 1.31 (S.D. = 0.15, $n = 13$) and 1.20 (S.D. = 0.10, $n = 11$) for the olanzapine and the risperidone group, respectively. This difference between groups was also not significant (Mann–Whitney $U = 41.5$, $P = 0.082$).

To enable direct comparison with other studies, we also specified two subgroups of patients with the clinically most prescribed doses, one group with olanzapine 15 mg ($n = 9$) and one group with risperidone 4 mg ($n = 8$). In the subgroup treated with 15 mg of olanzapine, the mean [^{123}I]IBZM binding ratio was 1.35 (S.D. = 0.14), corresponding to an occupancy of 62% (S.D. = 15). In the subgroup with 4 mg of risperidone, the mean [^{123}I]IBZM binding ratio was 1.19 (S.D. = 0.12), corresponding with an occupancy of 79% (S.D. = 13). This difference in [^{123}I]IBZM binding ratio was statistically significant. (Mann–Whitney $U = 12.5$, $P = 0.024$).

A negative linear correlation ($r = -0.551$, $P < 0.01$) was found between the olanzapine dose and the [^{123}I]IBZM binding ratio (Fig. 3). When olanzapine was converted to milligram per kilogram body weight, this remained significant ($r = -0.509$; $P < 0.01$). In the risperidone group, eight out of 13 patients were treated with 4 mg (Table 1). Therefore, a dose–occupancy correlation was not calculated.

3.2. PRL

PRL was elevated in all patients with risperidone ($n = 12$, all males; Fig. 4). In the olanzapine group, PRL was slightly elevated in three out of 15 patients, two males (19.5 μg/l and 21.0 μg/l) and one female (23.0 μg/l) (Fig. 4). The striatal [^{123}I]IBZM binding in both groups was not significantly different ($P = 0.07$). However, lower ratios of [^{123}I]IBZM binding correlated negatively with PRL levels in patients treated with olanzapine ($r = -0.551$; $P < 0.01$). We did not find a clear-cut break-off point for PRL elevation in this group. However, all three patients with slight PRL elevation had [^{123}I]IBZM binding ratios over 1.23 (corresponding occupancy of 74.6%). The correlation of [^{123}I]IBZM binding and PRL levels

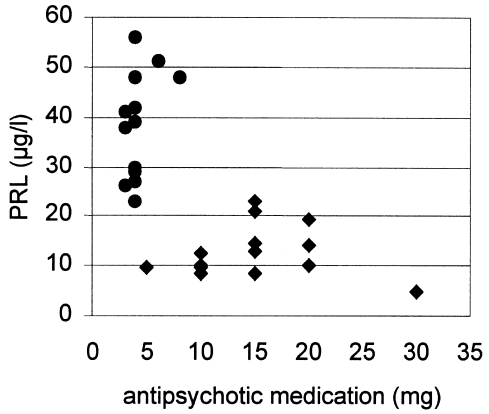

Fig. 4. Prolactin (PRL) levels (µg/l) in patients treated with various dosages of olanzapine (♦) or risperidone (●).

was not significant in the risperidone-treated group.

3.3. EPS

Mild to moderate akathisia was scored in 25% of the patients (nine out of 35). The Barnes akathisia rating scores showed a significant negative correlation with [^{123}I]IBZM binding ratio ($r = -0.417$, $P < 0.01$). When corrected for biperiden co-medication, this remained significant (multiple regression $\beta = -0.44$; d.f. = 32; $P = 0.011$). Olanzapine dose was positively correlated with akathisia rate ($r = 0.496$, $P < 0.05$). No significant correlation was found between akathisia rating and risperidone dose. No statistically significant difference in akathisia rating was found between patients treated with olanzapine (five positive out of 22) and risperidone (four out of 13) (t-test = -0.785; d.f. = 33; $P = 0.43$). No significant difference was found in SA or AIMS ratings between the two groups, and no significant correlation was found between [^{123}I]IBZM binding ratio and SA or AIMS score. Seven patients with risperidone were also treated with biperiden (Akineton).

3.4. PANSS

Positive symptoms of schizophrenia were significantly negatively correlated with the [^{123}I]IBZM binding ratio in the striatum ($r = -0.360$, $P < 0.05$) in the total group. No correlation was found between negative symptoms, general symptoms or depression and [^{123}I]IBZM binding ratio ($r = -0.134$, $P = 0.443$; $r = 0.048$, $P = 0.789$; $r = -0.220$, $P = 0.204$, respectively). The correlation between dose and positive symptoms was significant for risperidone ($r = 0.605$; $P < 0.05$), but not for olanzapine ($r = 0.375$; $P = 0.086$). No significant difference in PANSS scores was found between patients using olanzapine or risperidone at the moment of SPECT imaging. Both treatment groups were too small to include medication as a co-variable.

4. Discussion

In this clinical study we found no significant difference in occupancy of striatal DA D_2 receptors between the total olanzapine and risperidone groups, at a comparable clinical efficacy. However, when we studied subgroups of patients with the most prescribed doses, we found a significantly lower occupancy in patients treated with 15 mg olanzapine (62%) compared to patients treated with 4 mg risperidone (79%). This clearly demonstrates the influence of the composition of the groups that are under study. The high DA D_2 occupancy in the olanzapine-treated group is mainly caused by doses of 20 mg or more. In this dose range the DA D_2 occupancy is comparable to 4 mg of risperidone. Nevertheless, a large overlap in occupancy was found between olanzapine and risperidone.

We tried to explain the wide spread in levels of DA D_2 receptor occupancy, especially in patients treated with equal dosages. Our hypothesis was that patients with a more 'sensitive DA system' have a higher release of endogenous DA. This may explain the lower binding of [^{123}I]IBZM on comparable AP doses. However, with multiple regression analysis we found no significant influence of psychotic symptoms on [^{123}I]IBZM binding when corrected for AP dose. In individual patients who were outliners in the scatterplot of [^{123}I]IBZM binding and olanzapine dose, no cor-

relation with positive, negative or depressive symptoms could be found.

In this study, no plasma levels of AP were obtained. Therefore, correlations between plasma levels and DA D_2 receptor occupancy could not be made.

In line with our observations, Kapur et al. (1998, 1999) showed a comparable occupancy range of D_2 receptors by olanzapine and risperidone. Especially, the equal occupancy of risperidone and olanzapine at doses of 5 and 20 mg/day, respectively, is comparable to our findings in patients with 4 mg risperidone and 20 mg of olanzapine. The high occupancy of DA D_2 receptors in patients treated with olanzapine was confirmed in a PET study by Nordström et al. (1998). In contrast to our findings, a SPECT study by Pilowsky et al. (1996) showed a relatively low occupancy for olanzapine. This was more in the range of clozapine, as opposed to risperidone and classic AP. Nyberg et al. (1997) also found a relatively low occupancy (61%). The low occupancy of DA D_2 receptors reported by the last two mentioned studies may be explained by the low dosage of olanzapine.

Risperidone has been found to have a high DA D_2 receptor occupancy. Occupancy rates range in different studies from 66% with 2 mg (Kapur et al., 1995) to 99% with 10 mg (Knable et al., 1997). The 73% occupancy found by Kapur et al. (1995) at 4 mg is comparable to our finding of 79% at the same dose. A recent [^{123}I]IBZM SPECT study indicates a DA D_2 receptor occupancy of risperidone between haloperidol and clozapine (Dresel et al., 1998). Differences in occupancy rates are probably most dependent on dosage, imaging technique, and calculations.

To determine preclinical and clinical profiles of AP, Kapur (1998) suggests dividing AP into four groups: high and low D_2 and $5HT_2$ receptor occupancy. We found a high occupancy of the DA D_2 receptor by olanzapine and risperidone, placing both AP in the same group of high D_2 antagonists. The high $5HT_2$ in vivo receptor occupancy by olanzapine and risperidone has already been shown in different studies (Nyberg et al., 1997; Kapur et al., 1998; Travis et al., 1998).

Placing olanzapine and risperidone in a high D_2 receptor occupancy group, as opposed to clozapine, is in accordance with in vitro data (Bymaster et al., 1996).

The high occupancy of olanzapine and risperidone supports important aspects of the DA hypothesis of schizophrenia. The low DA D_2 receptor occupancy of clozapine is still one of the disturbing factors in this theory. However, interestingly, Seeman and Kapur (1997) shed new light on the supposed low binding of clozapine to the D_2 receptor. They show that clozapine also has a high in vivo occupancy of the D_2 receptor. This provides strong support for the DA hypothesis, according to which all AP mainly function through DA D_2 receptor antagonism.

To calculate the percentage of occupancy, we compared our patient [^{123}I]IBZM data to data obtained in normal control subjects. It might be more optimal to calculate the occupancy by comparing [^{123}I]IBZM binding in a drug-free and medicated state. However, several studies showed that the DA D_2 receptor density is not significantly different between drug-naive patients and normal control subjects (Farde et al., 1990).

A small number of patients were treated with benzodiazepines and SSRIs as concomitant medication at the moment of imaging. In a PET study, lorazepam has been shown to have no influence on striatal [^{11}C]raclopride binding (Hietala et al., 1997). In contrast to this, the SSRI citalopram has been shown to induce a slight decrease in striatal [^{11}C]raclopride binding (Tiihonen et al., 1996). However, in this study, statistical analysis showed no significant effect of the concomitant medication on [^{123}I]IBZM binding in the striatum. Moreover, after analysis of our data restricted to patients without SSRI and benzodiazepine, the conclusion that olanzapine and risperidone induced no significant difference in DA D_2 receptor occupancy remained intact. Finally, although a slight influence of SSRIs on striatal [^{123}I]IBZM binding could not be completely excluded, it was, from a clinical point of view, not possible to stop this medication at the moment of SPECT imaging.

4.1. PRL

We evaluated PRL levels after a stable dose period of 6 weeks or longer to exclude initial fluctuations. No baseline values for PRL were available, so it cannot be excluded that elevations in PRL had persisted from before treatment. Also, the phase of the menstrual cycle of the five participating female patients was not recorded. In this study, we found a significant difference of PRL levels in patients with olanzapine and risperidone. Atypical AP, like olanzapine, have been shown to induce smaller PRL elevations, which are often reversible, compared to typical AP (Beasley et al., 1996). In this study we found, in the olanzapine-treated group, higher PRL levels in patients with a higher DA D_2 receptor occupancy. Risperidone is considered an atypical AP, but increases PRL levels significantly more than olanzapine, and PRL remains more often elevated (Tran et al., 1997). There are several explanations for the difference in PRL levels in patients treated with olanzapine and risperidone. One explanation is a lower binding of olanzapine to the DA D_2 receptor compared to risperidone. This explanation is not supported by the results of this study. Secondly, the occupancy of DA D_2 receptors by olanzapine and risperidone might be different in the striatum and the pituitary. However, there are no studies to date that showed different DA D_2 receptors in these two regions. Nevertheless, it would be of interest to examine the DA D_2 receptor occupancy of AP in both striatum and pituitary with a radioligand with a higher affinity for extrastriatal DA D_2 receptors, e.g. [^{123}I]epidepride. Thirdly, Leysen et al. showed a different binding profile of olanzapine and risperidone for a serotonin receptor subtype. Olanzapine, as opposed to risperidone, proved to be a strong in vitro antagonist for the $5HT_{2C}$ receptor (Leysen et al., 1998). Blocking of the $5HT_{2C}$ receptor results in a suppression of PRL release (Coccaro et al., 1996). Thus, a difference in occupancy of the $5HT_{2C}$ receptor by olanzapine and risperidone may be the most likely explanation for the presently observed difference in PRL levels.

The postulated importance of a non-dopaminergic effect of AP in the hypothalamic/pituitary pathway may also play a major role in the mesolimbic/mesocortical DA pathway. To clarify differences in clinical response of AP, it may be essential to characterise also the in vivo binding to other neurotransmission systems than the dopaminergic system.

4.2. EPS

Although we found low to moderate scores of EPS in both patient groups, with no clear difference between groups, the akathisia rating was higher than expected. This rate of akathisia correlated positively with the DA D_2 receptor occupancy and with the dosage of olanzapine. This finding might be clinically relevant for dosing as low as possible to optimise compliance.

There are different explanations for the low incidence of EPS with olanzapine and risperidone. First, the DA D_2 receptor binding for most patients is just below the proposed crucial level of D_2 receptor occupancy above which EPS are thought to occur (Farde et al., 1992). Second, olanzapine is a strong muscarinic antagonist in vitro (Bymaster et al., 1996). Olanzapine may, therefore, function in vivo as a built-in anticholinergic agent. Third, mild EPS can also be a symptom of schizophrenia, as the rate of abnormal involuntary movements is not negligible in drug-naive first episode schizophrenic patients (Gervin et al., 1998). Finally, treatment with anticholinergic medication can mask EPS.

Interestingly, in this study we found a high correlation between different side effects. In line with this finding, patients who experienced side effects often had positive scores on all EPS scales.

Patients with higher scores on the positive items of the PANSS had a significantly lower [^{123}I]IBZM binding. This is likely to reflect the fact that this was not a fixed dose study, resulting in a significantly higher dose of AP in patients with more psychotic symptoms. An overall improvement in symptoms was registered in the period between intake and the moment of SPECT imaging. Because the patients used a variety of AP at intake, it was not possible to assess optimally the response to olanzapine or risperidone treatment.

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