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ORIGINAL INVESTIGATION

Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D_2 receptor occupancy in patients with schizophrenia

Ryosuke Arakawa · Hiroshi Ito · Akihiro Takano · Hidehiko Takahashi · Takuya Morimoto · Takeshi Sassa · Katsuya Ohta · Motoichiro Kato · Yoshiro Okubo · Tetsuya Suhara

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Abstract
Rationale Paliperidone ER is a novel antipsychotic drug in an extended-release (ER) formulation. As with all antipsychotics, careful dose setting is necessary to avoid side effects.
Objectives In this study, we measured striatal and extrastriatal dopamine D_2 receptor occupancy during paliperidone ER treatment in patients with schizophrenia using positron emission tomography (PET) to compare regional occupancy and to estimate the optimal dose.
Materials and methods Thirteen male patients with schizophrenia participated in this 6-week multiple-dose study. Six of them took 3 mg of paliperidone ER per day, four took 9 mg, and three took 15 mg. Two to 6 weeks after first drug intake, two PET scans, one with [^{11}C]raclopride and one with [^{11}C]FLB 457, were performed in each patient on the same day. The relationship between the dose or plasma concentration of paliperidone and dopamine D_2 receptor occupancy was calculated.
Results The dopamine D_2 receptor occupancies in the striatum measured with [^{11}C]raclopride and the temporal cortex measured with [^{11}C]FLB 457 were 54.2–85.5% and 34.5–87.3%, respectively. ED_{50} values of the striatum and temporal cortex were 2.38 and 2.84 mg/day, respectively. There was no significant difference in dopamine D_2 receptor occupancy between the striatum and the temporal cortex.
Conclusions The data from this study suggest that paliperidone ER at 6–9 mg provides an estimated level of dopamine D_2 receptor occupancy between 70–80% and that the magnitude of dopamine D_2 receptor occupancy is similar between the striatum and temporal cortex.

Keywords Paliperidone ER · Dopamine D_2 receptor occupancy · Striatum · Extrastriatum · Positron emission tomography · Schizophrenia

R. Arakawa · H. Ito · A. Takano · H. Takahashi · T. Morimoto · T. Suhara (✉)
Department of Molecular Neuroimaging, Molecular Imaging Center, National Institute of Radiological Sciences,
4-9-1, Anagawa, Inage-ku,
Chiba 263-8555, Japan
e-mail: suhara@nirs.go.jp

R. Arakawa · Y. Okubo
Department of Neuropsychiatry, Nippon Medical School,
Tokyo, Japan

T. Sassa
Asai Hospital,
Chiba, Japan

K. Ohta
Onda-daini Hospital,
Chiba, Japan

M. Kato
Department of Neuropsychiatry,
Keio University School of Medicine,
Tokyo, Japan

Introduction

Paliperidone is a novel antipsychotic drug for the treatment of schizophrenia. It is an active metabolite of risperidone (9-OH risperidone) and shows almost the same pharmacological profile, with high affinity for dopamine D_2 receptor and serotonin 5-HT_2 receptor (Leysen et al. 1988; Leysen et al. 1994). Paliperidone ER is the extended-release (ER) formulation of paliperidone, which offers low peak-to-trough

fluctuations, and a significant clinical effect over placebo has been reported (Davidson et al. 2007; Kane et al. 2007; Kramer et al. 2007).

Although the term 'limbic selectivity' has been attributed to second-generation antipsychotics based upon regional differences of dopamine D_2 receptor occupancy between the striatum and extrastriatal regions (Bigliani et al. 2000; Bressan et al. 2003a,b; Grunder et al. 2006; Kessler et al. 2006; Pilowsky et al. 1997; Stephenson et al. 2000; Xiberas et al. 2001), inconsistent results have been reported (Agid et al. 2007; Kessler et al. 2005; Talvik et al. 2001; Yasuno et al. 2001). There are no data in the literature concerning dopamine D_2 receptor occupancy in the striatum and extrastriatal regions by paliperidone.

In this study, we investigated the degree of dopamine D_2 receptor occupancy over a wide dose range of paliperidone ER (3–15 mg) and also compared the striatal and extrastriatal dopamine D_2 receptor occupancy in patients with schizophrenia using positron emission tomography (PET).

Materials and methods

Subjects and study protocol

Thirteen male patients (age range, 22–40 years; mean ± SD, 29.4±5.4 year) diagnosed with schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition criteria, participated in the study (Table 1). This study was conducted as part of an open-label phase II trial of paliperidone ER in Japan (JNS007ER-JPN-S21; Janssen Pharmaceutical K.K.). After complete explanation of the study, written informed consent was obtained from all patients. Exclusion criteria were current or past substance abuse, organic brain disease, epilepsy, or diabetes mellitus. Subjects with severe liver or renal dysfunction, prolonged QTc interval, and treatment with electroconvulsive therapy within 90 days before screening were also excluded. The inclusion criteria were less than 120 of the positive and negative symptom scale (PANSS) score at screening and patients well controlled by only one oral antipsychotic drug during the 4 weeks before the study. Administration of paliperidone ER started on the day after the last administration of the previous drug. The paliperidone ER dose was 3 mg/day in six patients, 9 mg/day in four patients, and 15 mg/day in three patients, given once a day after breakfast for 6 weeks at the same dosage. Clinical symptoms were assessed with PANSS before and 6 weeks after the start of treatment with paliperidone ER. Occurrence of extrapyramidal symptoms (EPS) was assessed by clinical observations without using the standard rating scale. After 2 to 6 weeks, two PET scans per patient were done on the same day, one with [^{11}C]raclopride for striatal dopamine D_2 receptor occupancy and one with [^{11}C]FLB 457 for extrastriatal dopamine D_2 receptor occupancy. The reason for the use of different radioligands was that [^{11}C]raclopride is suitable only for a high-density region such as the striatum, and [^{11}C]FLB 457 is suitable for a low-density extrastriatal region, but its affinity is too high for a high-density region (Ito et al. 1999; Okubo et al. 1999). This

Table 1 Characteristics of the patients, positive and negative symptom scale (PANSS), dopamine D_2 receptor occupancy, plasma concentration of paliperidone ER, and EPS

Patient number	Age (year)	Duration of illness (year)	PANSS		Dose (mg/day)	[^{11}C]raclopride		[^{11}C]FLB 457		EPS
			Before	After		Plasma concentration (ng/ml)	Receptor occupancy (%)	Plasma concentration (ng/ml)	Receptor occupancy (%)	
1	28	7.9	59	55	3	7.04	54.2	7.44	58.9	−
2	21	2.2	36	34	3	7.78	58.4	7.5	34.5	−
3	28	5.5	49	46	3	6.32	55.1	6.62	53.3	−
4	35	13	68	67	3	8.33	66.7	8.84	63.0	−
5	22	0.2	77	73	3	12.8	56.2	12.3	37.5	−
6	28	8.1	70	61	3	9.9	56.8	10.2	71.1	−
7	22	7.9	99	96	9	21.4	71.4	20.6	78.7	−
8	33	7.9	60	56	9	57	81.8	51.9	64.6	−
9	25	7.8	43	42	9	27.1	72.1	23.2	74.1	−
10	39	5.4	79	71	9	59.9	84.3	65.2	87.3	+
11	28	0.2	55	38	15	48.2	85.5	43.6	79.6	+
12	33	12.3	65	65	15	14.5	73.7	13.4	74.3	+
13	31	6.9	58	56	15	54.2	82.1	51.7	79.1	−
mean	29	6.6	62.9	58.5						
SD	5.4	3.9	16.5	16.8						

study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

PET procedure

A PET scanner system, ECAT EXACT HR + (CTI-Siemens, Knoxville, TN, USA), was used to measure regional brain radioactivity. To minimize head movement, a head fixation device (Fixter, Stockholm, Sweden) was used. A transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source before each scan. Dynamic PET scanning was performed for 60 min after intravenous bolus injection of 214.3–260.0 MBq of [^{11}C]raclopride. The specific radioactivity of [^{11}C]raclopride was 118.7–294.2 GBq/μmol (mean ± SD, 201.9±45.2 GBq/μmol). One hour after the end of the [^{11}C]raclopride PET measurement, dynamic PET scanning was performed for 80 min after intravenous bolus injection of 218.0–237.4 MBq of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 104.7–418.6 GBq/μmol (mean ± SD, 299.3±112.2 GBq/μmol). Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Gyroscan NT (Philips Medical Systems, Best, The Netherlands). T_1-weighted MR images at 1-mm slices were obtained. Venous blood samples were obtained immediately before tracer injection for each PET scan to measure the plasma concentration of paliperidone.

Data analysis

All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4. Regions of interest (ROIs) were defined for the striatum ([^{11}C]raclopride), temporal cortex ([^{11}C]FLB 457), and cerebellum ([^{11}C]raclopride and [^{11}C]FLB 457). The ROIs were drawn manually on the summated PET images with reference to the individual MR images. The average values of right and left ROIs were used for the analysis. Dopamine D_2 receptor binding was quantified using a three-parameter simplified reference tissue model (Ito et al. 2001; Lammertsma and Hume 1996). The cerebellum was used as the reference tissue given its negligible density of dopamine D_2 receptors (Suhara et al. 1999). This model allows the estimation of binding potential (BP_{ND}), which was defined as $f_{ND} \times B_{max}/K_d$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{max} is the receptor density, and K_d is the dissociation constant (Innis et al. 2007).

The dopamine D_2 receptor occupancy by paliperidone was estimated using the following equation: occupancy(%) = $(BP_{base} - BP_{drug})/BP_{base} \times 100$, where BP_{base} is the BP_{ND} in the drug-free state, and BP_{drug} is the BP_{ND} after administration of paliperidone (Takano et al. 2004; Takano et al. 2006a, b; Yasuno et al. 2001). In this study, the mean BP_{ND} in age-matched normal male subjects (n=13; age range 22–40 years; mean ± SD, 29.2±5.5 years) was used as BP_{base}, as BP_{ND} in the striatum measured with [^{11}C]raclopride or in the temporal cortex measured with [^{11}C]FLB 457 in patients with schizophrenia is not significantly different from that in the normal control (Farde et al. 1990; Suhara et al. 2002; Talvik et al. 2003). The PET procedure and data analysis for the BP_{ND} estimation of normal subjects were the same as those for the patients. The relationship between the dose or plasma concentration of paliperidone and dopamine D_2 receptor occupancy is described by the following equation: occupancy(%) = $C/(C + ED_{50}) \times 100$, where C is the dose or plasma concentration of paliperidone, and ED_{50} is the dose or plasma concentration required to induce 50% occupancy (Nyberg et al. 1999; Takano et al. 2004; Takano et al. 2006a, b; Yasuno et al. 2001). In this study, maximum occupancy was fixed at 100%, the same as previous occupancy studies of risperidone (Nyberg et al. 1999; Yasuno et al. 2001).

Measurement of plasma concentration of paliperidone

Blood samples were collected in heparinized tubes and centrifuged for 10 min at 3,000 rpm. Separated plasma samples were stored at −20°C. Plasma concentrations of paliperidone were determined using a validated liquid chromatography coupled to mass spectrometry/mass spectrometry (LC–MS/MS) method with a target lower limit of quantification of 0.10 ng/ml (Johnson & Johnson Pharmaceutical Research and Development L. L. C., Beerse, Belgium).

Statistical analysis

Correlations between dose or plasma concentration of paliperidone and dopamine D_2 receptor occupancy in the striatum and temporal cortex were assessed. Correlations between striatal occupancy and age or duration of illness were also assessed. Paired t tests were performed to compare (1) dopamine D_2 receptor occupancies between the striatum and temporal cortex and (2) plasma concentrations of paliperidone between the two PET scans, with [^{11}C]raclopride and [^{11}C]FLB 457, in each individual subject. In all tests, a p value<0.05 was considered statistically significant.

Results

The dopamine D_2 receptor occupancy in the striatum measured with [^{11}C]raclopride was 54.2 to 85.5% (Table 1). Mean dopamine D_2 receptor occupancies in the striatum were 57.9±4.5% at 3 mg/day, 77.4±6.6% at 9 mg/day, and 80.4±6.1% at 15 mg/day. ED_{50} in the striatum was 2.38 mg/day (r=0.86) and 6.65 ng/ml (r=0.82; Fig. 1).

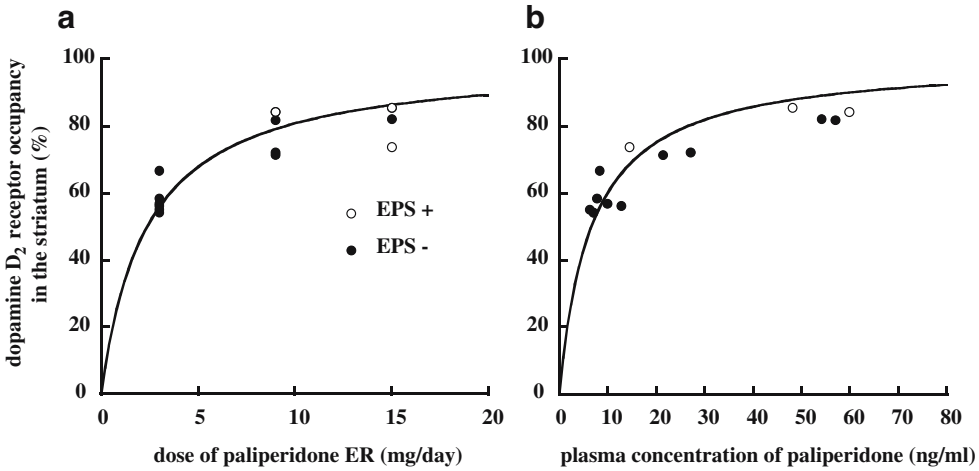

Fig. 1 Relationship between dopamine D_2 receptor occupancy in the striatum and dose (**a**) or plasma concentration (**b**) of paliperidone ER in the [^{11}C] raclopride study. ED_{50} in the striatum was 2.38 mg/day (r=0.86) and 6.65 ng/ml (r=0.82)

The dopamine D_2 receptor occupancy in the temporal cortex measured with [^{11}C]FLB 457 was 34.5 to 87.3%. Mean dopamine D_2 receptor occupancies were 53.1±14.5% at 3 mg/day, 76.2±9.5% at 9 mg/day, and 77.7±3.0% at 15 mg/day in the temporal cortex. ED_{50} in the temporal cortex was 2.84 mg/day (r=0.73) and 7.73 ng/ml (r=0.61; Fig. 2). There were no significant differences in plasma concentrations of paliperidone between the two scans (p=0.24) and in dopamine D_2 receptor occupancy between the striatum and temporal cortex at any dose (p=0.30).

There were no correlations between striatal occupancy and age (p=0.07) or duration of illness (p=0.90).

Average PANSS scores of all patients were 62.9±16.5 before taking paliperidone ER and 58.5±16.8 after 6 weeks. Three patients, two taking 15 mg and one 9 mg (no. 10, 11, 12), showed EPS (Table 1).

Discussion

The present study demonstrated that the ED_{50} of striatal dopamine D_2 receptor occupancy of paliperidone ER was 2.38 mg/day and that of the temporal cortex was 2.84 mg/day. Previous studies reported that the striatal ED_{50} of risperidone was 1.2 mg/day (Nyberg et al. 1999) and that the limbic-cortical ED_{50} was 1.46 mg/day (Yasuno et al. 2001). These studies indicate that the equivalent ratio for a daily dose between risperidone and paliperidone ER seems to be about 1:2. The striatal and temporal ED_{50} values of plasma concentration of paliperidone were 6.65 and 7.73 ng/ml, respectively, almost matching the values previously reported for risperidone active moiety (6.87 ng/ml, Nyberg et al. 1999; 7.43 ng/ml, Yasuno et al. 2001) for striatal and limbic–cortical regions, respectively. The therapeutic dose ranges of paliperidone ER calculated from ED_{50} were 5.6–9.5 mg/day and 15.5–26.6 ng/ml. In two previous studies (Nyberg et al. 1999; Yasuno et al. 2001), the sum of risperidone and paliperidone was regarded as risperidone active moiety. Because paliperidone shows almost the same affinity for dopamine D_2 receptor as risperidone, the effect for dopamine D_2 receptor was about the same between risperidone active moiety and paliperidone. This suggests that similar dopamine D_2 receptor occupancy is achieved with comparable plasma concen-

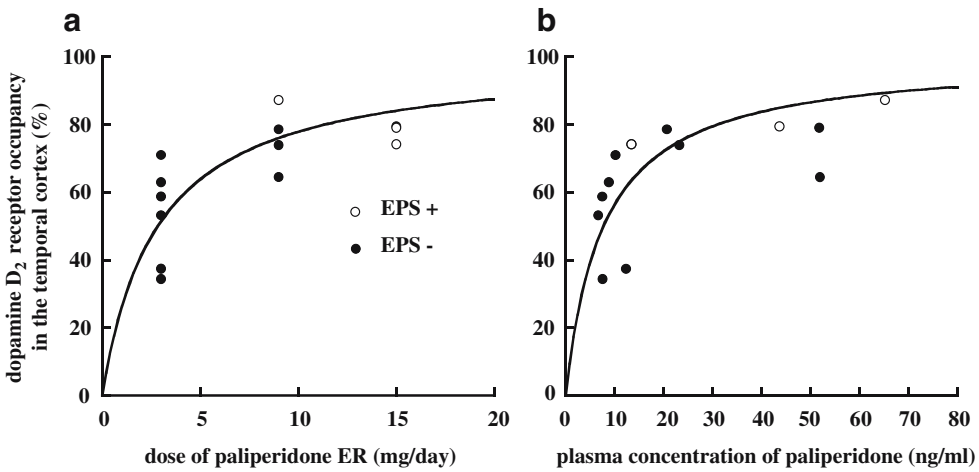

Fig. 2 Relationship between dopamine D_2 receptor occupancy in the temporal cortex and dose (**a**) or plasma concentration (**b**) of paliperidone ER in the [^{11}C]FLB 457 study. ED_{50} in the temporal cortex was 2.84 mg/day (r=0.73) and 7.73 ng/ml (r=0.61)

trations of paliperidone or risperidone active moiety. This finding confirms that paliperidone is as effective in crossing the blood–brain barrier as the active moiety of risperidone.

In the previous PET study that administered a single dose of paliperidone ER at 6 mg to four healthy Caucasian subjects, the striatal dopamine D_2 receptor occupancy fluctuation derived was 75–78%, and ED_{50} was 4.4 ng/ml (Karlsson et al., presented at WWS 2006). The differences between the two studies may be explained by the small number of observations and/or ethnicity. In the present study, occupancy was measured at steady-state drug levels (after multiple doses), whereas the previous study was carried out after a single dose.

There were no significant differences between striatal and extrastriatal dopamine D_2 receptor occupancy by paliperidone. Although the interval between the two scans was 2 h, the difference in plasma concentrations of paliperidone between them was about 7%, statistically not different as paliperidone ER tablets were made for flat plasma concentrations at a steady state. There have been discussions about the concept of 'limbic selectivity,' i.e., low dopamine D_2 receptor occupancy in the striatum and high occupancy in the extrastriatum (Pilowsky et al. 1997). It was reported in some second-generation antipsychotics such as clozapine (Grunder et al. 2006; Kessler et al. 2006; Pilowsky et al. 1997; Xiberas et al. 2001), olanzapine (Bigliani et al. 2000; Xiberas et al. 2001), amisulpiride (Bressan et al. 2003a; Xiberas et al. 2001), and quetiapine (Kessler et al. 2006; Stephenson et al. 2000) using [^{123}I] epidepride, [^{76}Br]FLB 457 or [^{18}F]fallypride. However, no significant difference between the striatum and extrastriatal regions have been reported using two different ligands, [^{11}C]raclopride and [^{11}C]FLB 457 (Agid et al. 2007; Talvik et al. 2001), or one ligand, [^{18}F]fallypride (Kessler et al. 2005). Human dopamine D_2 receptor occupancy by risperidone also showed inconsistent results. Two studies showed higher occupancy in the temporal cortex than in the striatum using [^{123}I]epidepride (75% in the temporal cortex and 50% in the striatum; Bressan et al. 2003b) and [^{76}Br] FLB 457 (91.6% in the temporal cortex and 63.3% in the striatum; Xiberas et al. 2001). On the other hand, similar occupancy values by risperidone were reported in the striatum (53–85%) using [^{11}C]raclopride (Nyberg et al. 1999) and extrastriatal regions (38–80%) using [^{11}C]FLB 457 (Yasuno et al. 2001). Because several factors such as scanning time, ligand selection, kinetic modeling, etc. need to be considered (Erlandsson et al. 2003; Olsson and Farde 2001), we used two different ligands to measure the different receptor density regions with appropriate scanning time and kinetic modeling for each ligand (Olsson and Farde 2001). Our results indicated no significant difference in regional occupancy (Agid et al. 2007; Kessler et al. 2005; Talvik et al. 2001; Yasuno et al. 2001). Although extrastriatal regions are suggested to be sites for antipsychotic action (Lidow et al. 1998), a recent study reported that extrastriatal dopamine D_2 receptor occupancy did not correlate with the antipsychotic effect (Agid et al. 2007).

In the present study, three patients complained of EPS. Average striatal occupancy of these three patients was 80.8%, a level in line with that known to increase the likelihood for EPS (Farde et al. 1992; Kapur et al. 2000; Nordstrom et al. 1993).

Previous studies indicated that over 70% of dopamine D_2 receptor occupancy is required for antipsychotic effects in patients with schizophrenia in the acute phase (Kapur et al. 2000; Nordstrom et al. 1993). In chronic treatment, haloperidol decanoate showed 73% occupancy at 1 week after injection and 52% occupancy at 4 weeks (Nyberg et al. 1995). Long-acting injectable risperidone showed 25–83 or 53–79% occupancy at a steady state (Gefvert et al. 2005; Remington et al. 2006). It is difficult to link the degree of dopamine D_2 receptor occupancy to a clinical effect, as almost all our patients (except nos. 5 and 11) had been undergoing long-term treatment when they entered the study. However, in all patients, these scores decreased with treatment or remained stable (Table 1) irrespective of dose. Furthermore, in all patients, striatal dopamine D_2 receptor occupancies above 50% were noted. This indicates that, for maintenance therapy of patients with schizophrenia, over 70% dopamine D_2 receptor occupancy might not necessarily be required. However, as this was an open-label study, further studies (such as randomized controlled trials) would be needed for an exact estimation of the threshold of dopamine D_2 receptor occupancy in the treatment of chronic patients with schizophrenia.

The half-life of paliperidone is about 28 h (data on file). High receptor occupancy is sustained when the plasma half-life of the treatment is long (Takano et al. 2004). Sustained high dopamine D_2 receptor occupancy can be expected at dosages of 9 or 15 mg/day of paliperidone ER. As EPS are a frequent reason for interruption of drug treatment (Lieberman et al. 2005), although the therapeutic dose range of paliperidone ER calculated from ED_{50} was 5.6–9.5 mg/day, for chronic treatment, lower doses might be useful, avoiding dopamine D_2 receptor occupancy rates above 80%. The estimated dopamine D_2 receptor occupancy at 6 mg/day of paliperidone ER was about 72%, in a range associated with efficacy (dopamine D_2 receptor occupancy above 70%) but not above a level associated with increased risks of extrapyramidal side effects (dopamine D_2 receptor occupancy above 80%).

To calculate the dopamine D_2 receptor occupancy in this study, we used BP_{ND} of normal control subjects as a surrogate for BP_{ND} in the drug-free state. Although previous studies showed no difference in dopamine D_2 receptor density in the striatum (Farde et al. 1990) or in the

temporal cortex (Suhara et al. 2002; Talvik et al. 2003) between the normal subjects and the patients with schizophrenia, individual differences in dopamine D_2 receptor density might potentially lead to an error in the estimation of dopamine D_2 receptor occupancy (Farde et al. 1992). For example, if BP_{base} changes from −13% to +15%, the range of the present study, the calculated 50% occupancy could be changed from 43 to 57%. The effect of a small portion of displaceable binding in the cerebellum (Delforge et al. 2001; Hall et al. 1996) may lead to an underestimation from 50% of [^{11}C]FLB 457 occupancy to 46% (Olsson et al. 2004). These factors may explain the differences in dopamine D_2 receptor occupancy between the striatum and temporal cortex in some patients.

Conclusions

The data from this study suggest that paliperidone ER at 6–9 mg provides an estimated level of dopamine D_2 receptor occupancy between 70–80%. The magnitude of dopamine D_2 receptor occupancy is similar between the striatum and temporal cortex.

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