Article

A PET Study Evaluating Dopamine D_2 Receptor Occupancy for Long-Acting Injectable Risperidone

Gary Remington, M.D., Ph.D., FRCPC

David Mamo, M.D., M.Sc., FRCPC

Alain Labelle, M.D., FRCPC

Jeffrey Reiss, M.D., FRCPC

Chekkera Shammi, M.B.B.S., FRCPC

Erik Mannaert, Ph.D.

Steve Mann, B.A.

Shitij Kapur, M.D., Ph.D., FRCPC

Objective: Long-acting injectable risperidone represents the first clinically available depot atypical antipsychotic. The present study used positron emission tomography (PET) to evaluate its dopamine D_2 binding profile at doses of 25, 50, or 75 mg administered every 2 weeks.

Method: After achieving stabilization with one of the doses, nine patients with a diagnosis of schizophrenia or schizoaffective disorder underwent [^{11}C]raclopride PET to measure D_2 occupancy. Participants were scanned twice during the 2-week injection interval: within 3 days after injection (postinjection) and within 5 days before the next injection (preinjection). At the same time, plasma was collected for measurements of risperidone plus 9-hydroxyrisperidone.

Results: Mean post- and preinjection D_2 occupancy levels for the 25-, 50-, and 75-mg doses were 71.0% and 54.0%, 74.4% and 65.4%, and 81.5% and 75.0%, respectively. There was a significant correlation between dose and plasma concentrations of risperidone plus 9-hydroxyrisperidone, and the estimated plasma concentration associated with 50% D_2 occupancy (ED_{50}) was 11.06 ng/ml. Prolactin levels were not correlated with drug levels or D_2 occupancy.

Conclusions: All three doses of injectable risperidone showed peak D_2 occupancy levels above the 65% threshold associated with optimal clinical response; the 75-mg dose approximated the 80% threshold linked to increased risk of extrapyramidal symptoms. Doses of 25 or 50 mg should provide therapeutic efficacy while minimizing the risk of extrapyramidal symptoms.

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Long-acting depot antipsychotics were introduced for clinical use in the 1960s, and among their advantages compared with oral agents was the greater assurance of medication delivery, reflected in decreased relapse rates (1, 2). While the use of depot antipsychotics varied between countries and settings (3, 4), they have proven to be a useful and important option in our treatment armamentarium (2, 5).

A shift in practice patterns took place in the 1990s with the influx of a number of novel antipsychotics, and the clinical advantages of these newer "atypical" agents rapidly positioned them as the treatment of choice for psychotic conditions such as schizophrenia (6–8). Despite their identified benefits, however, adherence has remained an issue (9, 10).

It is only recently, with the introduction of long-acting, injectable risperidone, that clinicians have had access to a depot atypical antipsychotic. This formulation represents an aqueous suspension that contains the drug in a matrix of glycolic acid-lactate polymer, and gradual hydrolysis of the copolymer at the injection site allows slow but steady release of risperidone over several weeks (11, 12). Various trials have indicated that it is an effective and well-tolerated treatment when administered every 2 weeks (13–16).

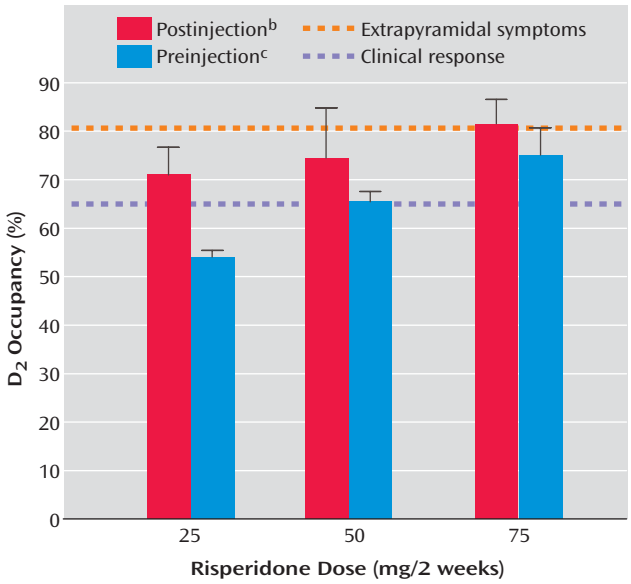
Positron emission tomography (PET) studies of antipsychotics, focusing in particular on dopamine D_2 receptor occupancy, have proven valuable in understanding the relationship between dose, clinical response, and D_2-related adverse events (e.g., extrapyramidal symptoms). Most of this work has involved oral antipsychotics (17–20), although at least one report with haloperidol decanoate has suggested that peak occupancies for the depot are in line with what is observed in oral formulations (21).

Building upon the existing clinical evidence for long-acting risperidone, we set out to evaluate the D_2 receptor occupancy of various doses using PET. The study was not designed as a clinical efficacy trial but rather was intended to provide occupancy data that, in the context of our current understanding, could provide additional in vivo evidence regarding appropriate dosing with this new formulation.

Method

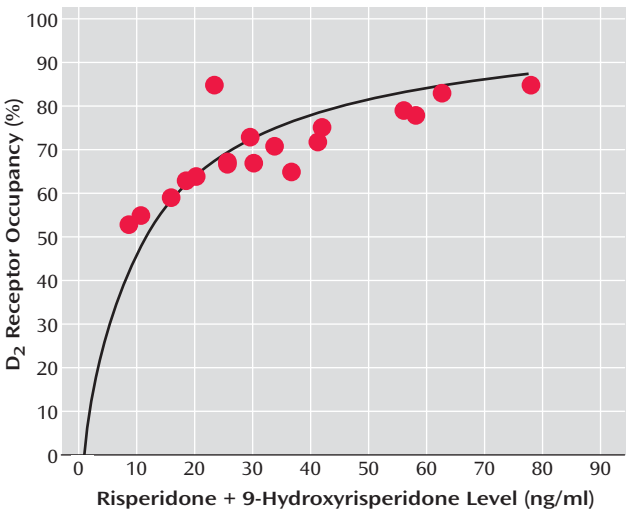
Subjects were recruited from a multicenter study investigating the use of long-acting risperidone administered every 2 weeks at three different doses (25, 50, or 75 mg) in individuals with schizophrenia or schizoaffective disorder (13). The PET investigation was approved by the Human Subjects Review Committee of the University of Toronto, and subjects provided written informed consent after receiving detailed information about the protocol.

FIGURE 1. Dopamine D_2 Receptor Occupancy Levels at Two Time Points Over the 2-Week Injection Interval for Nine Patients With Schizophrenia or Schizoaffective Disorder Receiving Long-Acting, Injectable Risperidone (25, 50, or 75 mg)[a]



[a] Hashed lines represent D_2 occupancy thresholds associated with clinical response and extrapyramidal symptoms from other reports (17, 18).
[b] Within 3 days after the injection.
[c] Within 5 days of the next injection.

FIGURE 2. Relationship Between D_2 Receptor Occupancy and Plasma Risperidone Plus 9-Hydroxyrisperidone Levels in Nine Patients With Schizophrenia or Schizoaffective Disorder Receiving Long-Acting, Injectable Risperidone (25, 50, or 75 mg) Every 2 Weeks[a]



[a] The regression line was fit to the following rectangular hyperbolic equation: occupancy=$\alpha \times$ [plasma level/(plasma level plus ED_{50})], where α is the maximal receptor occupancy, and ED_{50} is the plasma risperidone plus 9-hydroxyrisperidone level resulting in 50% maximal receptor occupancy. Maximal occupancy α was constrained to 100% to reflect the expected maximal occupancy at higher plasma levels. Each subject is represented by two points, representing the two scans carried out over the course of an injection interval.

Details of the multicenter trial have been published elsewhere, including design and clinical results (13). Briefly summarizing, patients were candidates for a switch to long-acting risperidone if they met DSM-IV criteria for schizophrenia or schizoaffective disorder and had been stabilized on an oral antipsychotic regimen for at least 4 weeks. Exclusion criteria were current treatment with clozapine, presence of DSM-IV-defined substance abuse or dependence within the preceding 3 months, a neurological or medical condition that could adversely influence patient safety or evaluation, pregnancy, demonstrated lack of response to oral risperidone in the past, or concomitant medications that could compromise D_2 evaluation (e.g., nonantipsychotic agents with dopamine agonist or antagonist properties).

During a 2-week run-in phase, antipsychotics other than oral risperidone were discontinued and replaced with oral risperidone at flexible doses ranging from 1 to 6 mg/day. Thus, all subjects were receiving oral risperidone during this phase, and the dose of long-acting risperidone that they received thereafter was dependent on the oral risperidone dose at the end of the run-in phase. Specifically, they were assigned to one of the three doses of long-acting risperidone as follows: those receiving 1–2 mg/day or 3–4 mg/day of oral risperidone were assigned to the 25-mg and 50-mg doses of long-acting risperidone, respectively; subjects assigned to the 75-mg dose of long-acting risperidone were those receiving 5–6 mg/day of oral risperidone. Supplementary oral risperidone doses (1–6 mg/day) could be used for the first 2–3 weeks following the switch, although this was not required in any of the cases reported here.

Long-acting risperidone was administered every 2 weeks, and at least five consecutive injections were administered before PET was carried out. Participants were scanned twice during the 2-week injection interval: within 3 days following injection (postinjection) and within 5 days before the next injection (preinjection).

D_2 occupancy was established using [^{11}C]raclopride following the same procedure employed at our center and detailed previously (22). PET scanning was conducted using a GEMS PC2048-Plus PET scanner (GE Medical Systems, Milwaukee) that produced 15 slices (thickness: 6.5 mm) with a resolution of about 5–6 mm in air. Patients were scanned lying down, with fixation of their heads achieved by use of a thermoplastic face mask (Tru-Scan Imaging, Annapolis, Md.).

Following injection of 10 mCi of high-specific-activity [^{11}C]raclopride (>300 Ci/mmol) using a bolus plus infusion protocol (23–26), a series of emission scans were obtained for 75 minutes. The regions of interest were the caudate/putamen, with the cerebellum used as a reference region. The regions of interest were drawn directly on averaged PET images and transferred to the dynamic PET images to obtain a time activity curve. An average of the striatum/cerebellum ratio minus one obtained between 30 and 75 minutes of scanning was taken as a measure of the equilibrium binding potential (27). Receptor occupancy was then calculated as the percentage reduction of receptor binding potential with drug treatment relative to baseline, using age-corrected measures of binding potential from a previously collected dataset of unmedicated comparison subjects obtained with a similar methodology. This comparison group consisted of 22 healthy subjects and nine antipsychotic-naive patients with a diagnosis of schizophrenia or schizophreniform disorder (mean age=31.5 years, SD=8.51, range=19–47). Since the mean binding potential in the healthy subjects (mean=2.7, SD=0.4) did not differ significantly from that of the antipsychotic-naive subjects (mean=2.9, SD=0.4) ($t=0.98$, $df=29$, $p=0.30$), the data from the two groups were combined to obtain the regression equation for the age-matched estimate of binding potential in the occupancy calculation (binding potential=age $\times 0.03 + 3.8$; $R^2=0.6$).

TABLE 1. Individual D_2 Occupancy, Risperidone Plus 9-Hydroxyrisperidone, and Prolactin Levels at Two Time Points Over the 2-Week Injection Interval for Nine Patients With Schizophrenia or Schizoaffective Disorder Receiving Long-Acting, Injectable Risperidone (25, 50, or 75 mg)

				Time Point During 2-Week Injection Interval[a]					
				Postinjection			Preinjection		
Patient	Gender	Age (years)	Dose (mg)	D_2 Receptor Occupancy[b] (%)	Risperidone Plus 9-Hydroxyrisperidone (ng/ml)	Prolactin[c] (µg/ml)	D_2 Receptor Occupancy[b] (%)	Risperidone Plus 9-Hydroxyrisperidone (ng/ml)	Prolactin[c] (µg/ml)
1	M	23	25	75	41.5	32	53	8.2	20
2	F	35	25	67	25.2	141	55	10.4	90
3	M	45	50	85	22.8	18	64	19.8	19
4	M	21	50	59	15.5	26	63	18.1	21
5	M	46	50	72	40.9	11	65	36.2	12
6	M	34	50	83	62.6	35	67	29.7	18
7	M	38	50	73	29.1	55	68	25.2	54
8	F	24	75	85	77.7	93	79	55.7	112
9	M	43	75	78	58.1	103	71	33.3	98

[a] Postinjection: within 3 days after the injection; preinjection: within 5 days of the next injection.
[b] Determined through a [^{11}C]raclopride PET scan.
[c] Normal values: male=3–13 µg/liter; female=3–27 µg/liter.

Venous blood was drawn for drug and prolactin concentrations at the time of the PET scans. For risperidone, blood samples were collected in heparinized tubes and centrifuged for 10 minutes at 2500 rpm within 2 hours of collection. Separated plasma was stored at –20°C for transport, and concentrations of risperidone plus 9-hydroxyrisperidone were determined by means of a validated radioimmunoassay method (11). Prolactin levels were determined by using a two-site chemiluminometric immunoassay with a minimal detectable limit of 0.3 ng/ml and a coefficient of variance of 3.6%–4.5% (ACS, CIBA-Corning Diagnostics, East Walpole, Mass.).

Statistical analyses were carried out using SPSS (SPSS Inc., Chicago). Bivariate correlation analysis was used to examine the relationship between the primary variables of interest. Nonlinear regression analysis was used in the estimation of plasma risperidone plus 9-hydroxyrisperidone level associated with 50% D_2 receptor occupancy.

Results

Nine participants (seven men and two women) completed the study. The group's mean age was 34 years (SD=9, range=21–46), and the dosage breakdown was as follows: 25 mg (N=2), 50 mg (N=5), and 75 mg (N=2).

As seen in Figure 1, D_2 occupancy levels, measured at the two time points (postinjection and preinjection) over the 2-week injection interval, increased in a dose-dependent fashion (25 mg: mean=71.0% [SD=5.7] and 54.0% [SD=1.4], respectively; 50 mg: mean=74.4% [SD=10.4] and 65.4% [SD=2.1]; 75 mg: mean=81.5% [SD=5.0] and 75.0% [SD=5.7]). Conversely, a comparison across all doses over the two time points indicated a significant reduction in both D_2 occupancy (t=3.67, df=8, p=0.006) and plasma concentrations of risperidone plus 9-hydroxyrisperidone (t=3.35, df=8, p=0.01). Eight of nine participants showed an expected decline in both of these measures over the course of the injection interval (Table 1). One participant showed a small increase in occupancy that paralleled a modest increase in plasma levels (patient 4), but given the test-retest standard deviation of 6% in our lab this change is not significant.

Dose showed a significant correlation with plasma risperidone plus 9-hydroxyrisperidone concentrations (r=0.63, df=7, p=0.006), even after we controlled for time (r=0.69, p=0.002). The relationship between plasma concentration and D_2 occupancy was captured by a saturating hyperbola (B_{max} constrained to 100%), with the estimated plasma concentration associated with 50% D_2 occupancy (ED_{50}) being 11.06 ng/ml (95% confidence interval=9.15–12.96) (Figure 2).

Mean prolactin values at the two time points (postinjection and preinjection) over the 2-week injection interval were 57.11 µg/liter (SD=44.97) and 44.59 µg/liter (SD=38.30), respectively, representing a nonsignificant difference (t=0.74, df=23, p=0.47). There was no significant correlation between prolactin concentrations and plasma concentrations of risperidone plus 9-hydroxyrisperidone (r=0.32, p=0.12) or D_2 receptor occupancy (r=0.34, p=0.10).

We sampled only a small subgroup of the larger clinical sample, and the specific findings of the latter have been reported elsewhere (13). All subjects participating in the PET study either remained stable or showed clinical improvement during the trial, with the exception of one individual (patient 8) who showed a 1-point Clinical Global Impression deterioration. Extrapyramidal symptom scores, as measured by the Extrapyramidal Symptom Rating Scale, remained low in all dose groups throughout the PET study.

Discussion

With any new medication, it is critical that guidelines regarding optimal dosing be established. Previous PET data have indicated that optimal clinical response occurs when at least 65% of striatal D_2 receptors are occupied, while the risk of extrapyramidal symptoms increases notably at D_2 occupancy levels above 80% (17, 18). The present findings indicate that long-acting injectable risperidone, even at a dose of 25 mg every 2 weeks, exceeds the threshold associ-

ated with clinical response. As expected, D_2 occupancy was dose-dependent, with only the highest dose employed (75 mg) approximating the threshold that has been associated with extrapyramidal symptoms in previous studies.

These findings suggest that for most patients treated with long-acting risperidone, clinical efficacy should be expected at doses of 25–50 mg. This corroborates the existing clinical evidence showing no additional clinical benefit at higher doses (14). Moreover, our PET results suggest that dosing at 75 mg every 2 weeks may be associated with some degree of increased risk of extrapyramidal symptoms, supporting the observation of a dose-dependent risk of extrapyramidal symptoms in the clinical setting (14).

Mean D_2 occupancy levels toward the end of the injection interval for the 50- and 75-mg doses exceeded 65%, while for the 25-mg dose the end-of-interval occupancy level was 54%. At first glance, these data might be seen as suggesting that individuals receiving 25 mg would be vulnerable to relapse toward the end of the injection interval. However, maintenance of D_2 occupancy levels above the 65% threshold may not be necessary for clinical response. It has been shown, for example, that individuals can be stabilized on a regimen of haloperidol decanoate administered every 4 weeks, despite mean D_2 occupancy levels decreasing from 73% (range=60%–82%) at week 1 to 53% (range=20%–74%) at week 4 (21). Indeed, there is a growing body of evidence to suggest that there may be clinical advantages to avoiding sustained, high D_2 blockade (28).

Previous work from our center with oral risperidone, which evaluated the relationship between D_2 occupancy and risperidone plus 9-hydroxyrisperidone, established an ED_{50} of 6.08 ng/ml (95% CI=4.8–7.3) (29). In contrast, the calculated ED_{50} here was 11.06 ng/ml (95% CI=9.15–12.96). This discrepancy may reflect study group size: in the first report the curve was established based on nine data points, including one significant outlier, whereas the current estimate was constructed from twice as many data points. There are well-recognized concerns regarding the impact of inter- and intraindividual variability in plasma antipsychotic levels and efforts to establish "therapeutic windows" (30–32). Bearing in mind this caveat, the current estimate actually dovetails nicely with a more recent review of this topic suggesting an optimal therapeutic range for risperidone plus 9-hydroxyrisperidone of 20–60 ng/ml (33). As seen in Figure 2, 20 ng/ml is associated with 65% D_2 occupancy, while 60 ng/ml represents 84% D_2 occupancy. Thus, the lower level meets the threshold associated with optimal clinical response, whereas the upper limit is just over the threshold linked to increased extrapyramidal symptom risk (18), which in turn may compromise clinical outcome.

The lack of correlation between prolactin and D_2 occupancy was not entirely unexpected, since factors mediating prolactin secretion are complex (34). Our own examination of this issue has in the past provided mixed results (17, 22), and efforts to establish a threshold for hyperprolactinemia in the same fashion as clinical response and extrapyramidal symptoms have not met with the same degree of agreement (17, 35).

A comment is warranted regarding timing of the PET scans in this study and the actual pharmacokinetics of long-acting risperidone. The two points used here were chosen to reflect the time frame of the recommended 2-week injection interval, and in so doing provide a reflection of occupancy through the cycle of treatment at steady state. This needs to be distinguished, however, from the actual pharmacokinetics of single- and multiple-dose long-acting risperidone (11). According to single-dose data an injection's peak occurs approximately 4–6 weeks later, meaning that the main release phase is not observed until after several injection intervals. Over the course of an injection interval at steady state, concentrations of the active moiety (C_{max} to C_{min}) decrease by approximately 50%–60%, and while this rate of decrease is notably greater than what is observed in terms of changes in D_2 occupancy, we are reminded that a significant dissociation between brain and plasma kinetics in this regard has been reported with antipsychotics (36).

At least several limitations qualify our conclusions. PET studies of this sort involve limited numbers of patients, much smaller than what would be required to definitively analyze the relationship between dose/receptor occupancy and response/side effects. As a result, to make clinical inferences we must extrapolate the D_2 occupancy data to other larger clinical trials (13, 14). In addition, by focusing on the D_2 story we do not address the potential contribution of other receptors and systems in a class of medications that are best characterized by their pharmacological heterogeneity (37–39). Even confining our comments to D_2, the use of [^{11}C]raclopride as the ligand focuses on striatal D_2 receptor occupancy. However, it can be argued that D_2 receptor occupancy in other areas is involved in clinical response and that, further, there is evidence that atypical agents may show differential D_2 occupancy between striatal and extrastriatal regions (40–47). However, having raised each of these concerns, we are somewhat reassured by the fact that the present data are in line with existing clinical trial and plasma drug data (13, 14, 33) as well as recently published PET data from another center (48).

In this particular study, patients were first switched to oral risperidone and then to the depot risperidone formulation on the basis of the final oral dose. Establishing comparable doses between the two formulations is complicated by the more complex pharmacokinetics of long-acting risperidone and differences in bioavailability. However, the PET data now available lend support to the position that long-acting risperidone doses of 25–75 mg are in line with oral risperidone doses of 2–6 mg (48).

In summary, the PET findings reported here support available clinical evidence indicating that dosing long-acting risperidone at 25–50 mg every 2 weeks is sufficient in attaining clinical response with minimal risk of extrapyrami-

dal symptoms. In addition, they provide further data regarding the relationship between plasma drug levels and D_2 occupancy. Having this information may assist clinicians as they familiarize themselves with long-acting injectable risperidone and incorporate it into their clinical practice.

Received Jan. 19, 2005; revision received April 18, 2005; accepted May 13, 2005. From the Schizophrenia Program, Centre for Addiction and Mental Health. Address correspondence and reprint requests to Dr. Remington, Schizophrenia Program, Centre for Addiction and Mental Health, 250 College St., Toronto, Ont. M5T 1R8, Canada; gary_remington@camh.net (e-mail).

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