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A PET Study of 5-HT_2 and D_2 Dopamine Receptor Occupancy Induced by Olanzapine in Healthy Subjects

Svante Nyberg, M.D., Ph.D., Lars Farde, M.D., Ph.D., and Christer Halldin, Ph.D.

Olanzapine is a new antipsychotic drug with affinity for 5-HT_2, D_2, D_1, and muscarinic receptors. Positron emission tomography and the radioligands [^{11}C]raclopride and [^{11}C]NMSP were used to measure D_2 and 5-HT_2 receptor occupancy in three healthy subjects after 10 mg olanzapine orally. After seven hours D_2 receptor occupancy was 63%, 62% and 59%, respectively. After 9.5 hours 5-HT_2 receptor occupancy was 74%, 86% and 92%. D_2 and 5-HT_2 receptor occupancy was comparable to that found in patients continuously treated with clozapine. Clinical efficacy has been demonstrated for olanzapine in the dose range 5 to 15 mg per day. Extrapolation from our present observations after a 10 mg single-dose suggest, that at the lower end of the clinically examined dose range the D_2 and 5-HT_2 receptor occupancy should be similar to that induced by standard doses of clozapine. Detailed evaluation of the dose-response characteristics of olanzapine and direct clinical comparison to clozapine will thus provide valuable leads to the clarification of atypical antipsychotic action. **© 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16:1–7, 1997]**

KEY WORDS: *Positron emission tomography; human; D_2 dopamine receptors; 5-HT_2 receptors; olanzapine; antipsychotic drugs; atypical*

The hypothesis that the antipsychotic effect of classical neuroleptics is induced by blockade of D_2-like dopamine receptors has been supported by several studies with positron emission tomography (PET). Clinical treatment with all currently used chemical classes of classical neuroleptics induces a uniformly high (70–89%) degree of central D_2 dopamine receptor occupancy (Farde et al. 1992).

The support for an important role of the central D_2 receptor does not preclude that antipsychotic effect may be induced or enhanced by drugs acting on other neurotransmitter systems. Among several proposed mechanisms, 5-HT_2 receptor antagonists have been in focus of attention during recent years. It has been proposed that the clinical properties of the "atypical antipsychotic" clozapine is explained by its simultaneous interaction with 5-HT_2 and D_2 receptors (Meltzer et al. 1989; Meltzer 1991). Clozapine has been described as "atypical" because it has a very low tendency to induce acute extrapyramidal syndromes (EPS) in man, and is effective in patients treatment-refractory to classical neuroleptics (Kane et al. 1988). In PET studies, clozapine's *in vitro* affinity for 5-HT_2 receptors is reflected in a very high (85–90%) 5-HT_2 receptor occupancy in patients treated with low to moderate doses of clozapine (Nordström et al. 1995b). In contrast, the D_2 receptor occupancy in clozapine-treated patients was clearly lower (20–67%) than in patients treated with classical neuroleptics (Farde et al. 1992; Nordström et al. 1995b).

Olanzapine is a new antipsychotic drug. Binding studies *in vitro* on both rodent and human brain receptors have shown that the binding profile of olanzapine was similar to that of clozapine. Olanzapine has affinity

From the Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, Stockholm, Sweden.

Address correspondence to: Svante Nyberg, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, S-171 76 Stockholm, Sweden.

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for dopamine D_1, D_2, D_4, serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, α_1-adrenergic, histamine H_1 and five muscarinic receptor subtypes (Bymaster et al. 1995). *In vivo* animal studies have indicated that olanzapine is a dopaminergic, serotonergic and muscarinic receptor antagonist (Fuller and Snoddy 1992; Moore et al. 1992; Moore et al. 1994). On the basis of these results, it has been suggested that olanzapine may have the profile of an "atypical" antipsychotic in the treatment of schizophrenia.

Preliminary studies in healthy volunteers and schizophrenic patients have indicated that olanzapine is safe and well tolerated. Dose-dependent sedation was the main side-effect (data on file, Eli Lilly Research Laboratories, Indianapolis, USA). In a single-dose pharmacokinetic study in healthy subjects the reported time to peak plasma concentration (T_{max}) was 5 hours, and the elimination half-life was 29 hours (Nyhart et al. 1995). A recent controlled study in schizophrenic patients has demonstrated antipsychotic efficacy in the dose range 5–15 mg per day (Beasley et al. 1995).

The objective of this PET study was to measure the D_2 dopamine and 5-HT_2 receptor occupancy induced by a single oral dose of 10 mg olanzapine. The dose was chosen to be within a suggested clinically effective dose range, and since this dose had been well tolerated in previous single-dose studies in healthy men. Of particular interest was to determine whether olanzapine, like clozapine, induces a higher occupancy of 5-HT_2 than D_2 receptors.

SUBJECTS AND METHODS

The study was approved by the Ethics and the Radiation Safety Committees of the Karolinska Hospital, and the Medical Products Agency of Sweden. The subjects were examined at the Department of Clinical Neuroscience, Karolinska Hospital.

Subjects

Three male volunteers aged 33, 26 and 23 years were recruited after giving their informed consent. Their body weight and length was 78 kg/181 cm, 71 kg/182 cm, and 85 kg/177 cm, respectively. They were healthy according to history, physical examination, psychiatric interview, blood and urine analyses, computerized tomography (CT) of the brain, and a standard 12-lead ECG.

Several antipsychotic drugs are sensitive to the debrisoquin hydroxylation type genetic polymorphism (Dahl and Bertilsson 1993). To exclude subjects with poor metabolic capacity as a potential source of variability, a debrisoquin hydroxylation test was performed in each subject according to (Sanz et al. 1989). The metabolic ratio (MR) of debrisoquin was defined as the ratio of recovery in the urine of debrisoquin to that of the 4-hydroxyl metabolite determined over a period of 8 hours after an oral dose of 10 mg debrisoquin. All three subjects were characterized as "extensive metabolizers" (Alván et al. 1990), with metabolic ratios of 0.30, 0.18 and 0.13, respectively.

Design and Drug Administration

This open exploratory study was performed on two experimental occasions in each of three healthy subjects. Two consecutive PET experiments were conducted on each occasion for determination of D_2 and 5-HT_2 receptor binding, respectively. On the first day experiments were performed to establish baseline. On the second day, 10 mg olanzapine was administered as oral tablets to fasting subjects at 6 AM. After drug administration PET experiments were started at 7 hours to measure D_2 receptor occupancy and at 9.5 hours to measure 5-HT_2 receptor occupancy. The times of the PET experiments were chosen to be at high and comparable plasma concentrations, thus starting two hours after the predicted T_{max} (Figure 1). No concomitant medication was given.

Olanzapine Plasma Concentrations

Blood samples (10 mL) for the measurement of plasma olanzapine concentrations were drawn from a cubital vein into heparin-treated glass tubes, then centrifuged and plasma was frozen at −20°C until analyzed. Samples were collected every hour for the first 12 hours and at 26 hours. Plasma olanzapine was analyzed by an HPLC method with electrochemical detection by Eli Lilly Research Laboratories (Catlow et al. 1995). The limit of quantification was 0.25 ng/mL.

Pharmacodynamics

At the second experimental occasion, the subjects stayed in the research ward under continuous observation from 8 PM the night before administration of olanzapine to 8 AM the day after. Clinical pharmacodynamic effects were evaluated at baseline and 3, 6, 9, 12 and 26 hours after administration of olanzapine. Subjective experiences were noted on the basis of open questioning. EPS were rated according to "A rating scale for drug-induced akathisia" (Barnes 1989) and "A rating scale for extrapyramidal side effects" (Simpson and Angus 1970). Blood pressure and heart rate was measured with an electronic measuring device (Siemens Sirecust 630) after 5 minutes rest lying down. Orthostatic blood pressure and heart rate was measured immediately after standing up and after one minute.

PET Experimental Procedure

The PET-camera system Scanditronix PC2048-15B (General Electric, Uppsala, Sweden) was used to measure ra-

dioactivity in brain tissue after an i.v. bolus injection of radioligand in tracer doses. This PET camera consists of 8 rings with 256 detectors in each ring and measures radioactivity in 15 brain sections with a thickness of 6 mm each. The resolution of the reconstructed images is 4.5 mm (Litton et al. 1990). Radioactivity in the brain was measured for 51 minutes according to a preprogrammed sequence of 19 scans. To obtain uptake curves, regional radioactivity was calculated for each scan, corrected for decay and plotted versus time. For details on the experimental procedure, see (Farde et al. 1989; Nyberg et al. 1993).

Radioligands

The radioligands used were [^{11}C]raclopride for D_2 receptors and [^{11}C]NMSP for 5-HT_2 receptors. [^{11}C]raclopride was prepared as previously described (Halldin et al. 1991). The specific radioactivity at the time of injection was 5.8–31.3 GBq/μmol, and the radioactivity injected was 296–313 MBq.

To prepare [^{11}C]NMSP, [^{11}C]methyl iodide (Halldin et al. 1990) was trapped at room temperature in a reaction vessel (1.0 mL mini-vial, Alltech) containing 1.0 mg of spiperone, dimethylformamide (350 μL), and freshly prepared aqueous tetrabutylammonium hydroxide (TBAH, 0.4 M, 2.0 μL). The vessel was sealed and heated to 80°C for 1 min. HPLC mobile phase (650 μL) consisting of acetonitrile and 0.01 M phosphoric acid (35/65) was added before injection onto the semi-preparative HPLC column. [^{11}C]NMSP eluted between 8 and 10 min. Before evaporation, ethanol was added to the collected HPLC fraction to prevent radiolysis. After evaporation of the mobile phase the residue was dissolved in sterile phosphate buffered saline, pH = 7.4 (8 mL) and filtered through a Millipore filter (0.22 μm), yielding a solution which was sterile and free from pyrogens. The total radiochemical yield was 70–80% with a total synthesis time of 30 min. The radiochemical purity was better than 98%.

The preparation of [^{11}C]NMSP was based on the method described by Dannals et al. (1986). The method was modified because the reagent TBAH is unstable. Thus, TBAH was freshly prepared on the same day. Various amounts (1, 2, 5, 10, 15 and 20 μL) of TBAH were evaluated with respect to optimal incorporation of [^{11}C]methyl iodide into [^{11}C]NMSP. The best incorporation (>95%) was achieved with 2 μL. In our hands, the amount proscribed by Dannals et al. (1986) (10 μL) yielded an about 30% incorporation. Both methods gave the same quality of product, but present yield of the labeling reaction was higher and more reproducible.

The specific radioactivity at the time of injection of [^{11}C]NMSP was 10.4–70.1 GBq/μmol, and the radioactivity injected was 282–322 MBq. Thus, the total mass injected of both ligands was very low, and the receptor occupancy induced by the radioligands themselves negligible.

Regions of Interest

A head fixation system with individually made plastic helmets was used throughout, to avoid movement artifacts and to ensure that the same regions of interest could be used for all experiments in each subject (Bergström et al. 1981). The fixation system was also used in the initial morphological examination with computerized tomography (CT). The position of the foramen of Monro relative to the fixation system was determined with CT. Regions of interest were drawn on the reconstructed PET images from the baseline experiments. Regions were drawn bilaterally for the putamen in two adjacent sections, covering the level of the foramen of Monro. The frontal cortex region was drawn in six adjacent sections. Data from adjacent regions was pooled before calculation of regional radioactivity. The cerebellum region was drawn in one section.

Calculation of D_2 and 5-HT_2 Receptor Occupancy

The calculation of receptor occupancy was based on the theory for ratio-equilibrium analysis of D_2 receptor occupancy using [^{11}C]raclopride, which has previously been described in detail (Farde et al. 1988; Farde et al. 1989).

The cerebellum is a reference region with a negligible density of D_2 receptors (Hall et al. 1988). The total radioactivity in the cerebellum, $C_{cer}(t)$, was used as an estimate of the free and non-specifically bound radioligand concentration in the brain. Radioactivity representing ligand bound specifically to D_2 receptors, $C_b(t)$, was defined as

$$C_b(t)_{raclopride} = C_{put}(t) - C_{cer}(t) \qquad \text{(equation 1)}$$

where $C_{put}(t)$ is the regional radioactivity in the putamen.

The ratio of frontal cortical to cerebellar uptake of [^{11}C]NMSP was used to determine 5-HT_2 receptor occupancy, in analogy with the method described above for calculation of D_2 receptor occupancy (Nyberg et al. 1993). The density of 5-HT_2 receptors in the cerebellum is negligible (Schotte et al. 1983; Pazos et al. 1987). Therefore, also after injection of [^{11}C]NMSP the total radioactivity in the cerebellum, $C_{cer}(t)$ was used as an estimate of the free radioligand concentration in the brain. Radioactivity representing ligand bound specifically to 5-HT_2 receptors, $C_b(t)$, was defined as

$$C_b(t)_{NMSP} = C_{fr}(t) - C_{cer}(t) \qquad \text{(equation 1)}$$

where $C_{fr}(t)$ is the regional radioactivity in the frontal cortex.

The curves for $C_b(t)$ and $C_f(t)$ were integrated from 9 to 45 minutes after radioligand injection and a ratio R was obtained according to the equation

$$R = \int_9^{45} C_b(t) / \int_9^{45} C_f(t) \qquad \text{(equation 1)}$$

The integration was chosen to approximate the time of equilibrium for both radioligands. D_2 and 5-HT_2 receptor occupancy, respectively, was defined as the percent reduction in R after administration of olanzapine as compared to the baseline R value in the same subject in the absence of active drug. Thus, each subject was used as his own control.

RESULTS

Each subject completed the study according to the protocol. All PET experiments were started within 10 minutes of the schedule, 7 and 9.5 hours after administration of olanzapine. The plasma concentration curves of olanzapine were similar between subjects, and the concentrations were similar at the times of the two PET experiments in each subject (Figure 1). After the administration of olanzapine, there was a marked reduction of [^{11}C]NMSP binding in the neocortex (Figure 2). The calculated 5-HT_2 receptor occupancy was 74%, 86% and 92%, respectively (Figure 3). There was also a marked reduction in [^{11}C]raclopride binding in the putamen (Figure 2). The calculated D_2 receptor occupancy was 63%, 62% and 59%, respectively (Figure 3).

Neither extrapyramidal side effects nor akathisia were recorded. The subjects reported marked sedation during the first six hours after administration of olanzapine. All three subjects were drowsy, and fell asleep repeatedly during the day when not activated. There were no changes in blood pressure or pulse rate.

DISCUSSION

Three healthy men were examined with PET after 10 mg olanzapine as a single oral dose. The 5-HT_2 receptor occupancy was very high (74%, 86% and 92%), while D_2 receptor occupancy was 59%, 62% and 63%.

After the present single dose of olanzapine, the 5-HT_2 receptor occupancy was at the same level as that found in schizophrenic patients treated with clozapine (Farde et al. 1992; Nordström et al. 1995b) The D_2 receptor occupancy was within the higher range found in clozapine-treated patients (20–67%) and lower than the 70%–90% found in patients treated with classical antipsychotic drugs (Farde et al. 1992; Nordström et al. 1995b).

In this study, healthy subjects were examined to measure the receptor occupancy induced by a single dose of olanzapine. It can be questioned, if such results can be used to predict receptor occupancy induced by continuous treatment in schizophrenic patients. We have previously shown that there is no difference in [^{11}C]raclopride binding to central D_2 receptors in healthy subjects and drug-naive schizophrenic patients (Farde et al. 1990). Recently, we found no difference in the ratio of [^{11}C]NMSP binding in the frontal cortex to that in the cerebellum among 7 healthy subjects and 7 neuroleptic-naive schizophrenic patients (Nordström et al. 1995a). An important advantage with studies in healthy volunteers is that each subject can be examined in a drug-free condition and serve as his own control. This approach eliminates inter-individual variations in receptor numbers and distribution as a source of variability. Receptor occupancy measured in healthy subjects should be thus predictive to schizophrenic patients. According to the law of mass action the relation between receptor binding and the concentration of ligand at equilibrium is described by a hyperbolic function (Farde et al. 1989).

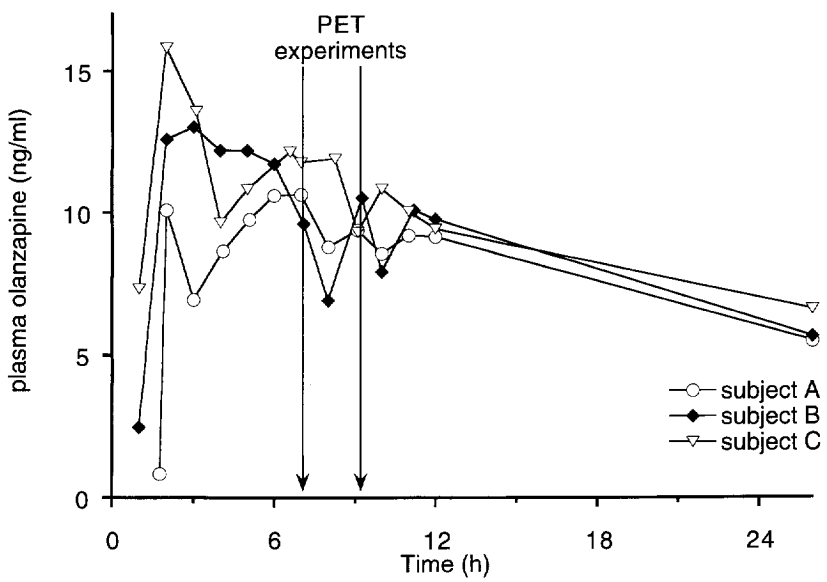

Figure 1. Plasma concentrations of olanzapine in three healthy subjects after administration of 10 mg olanzapine orally. The times of the PET experiments are indicated.

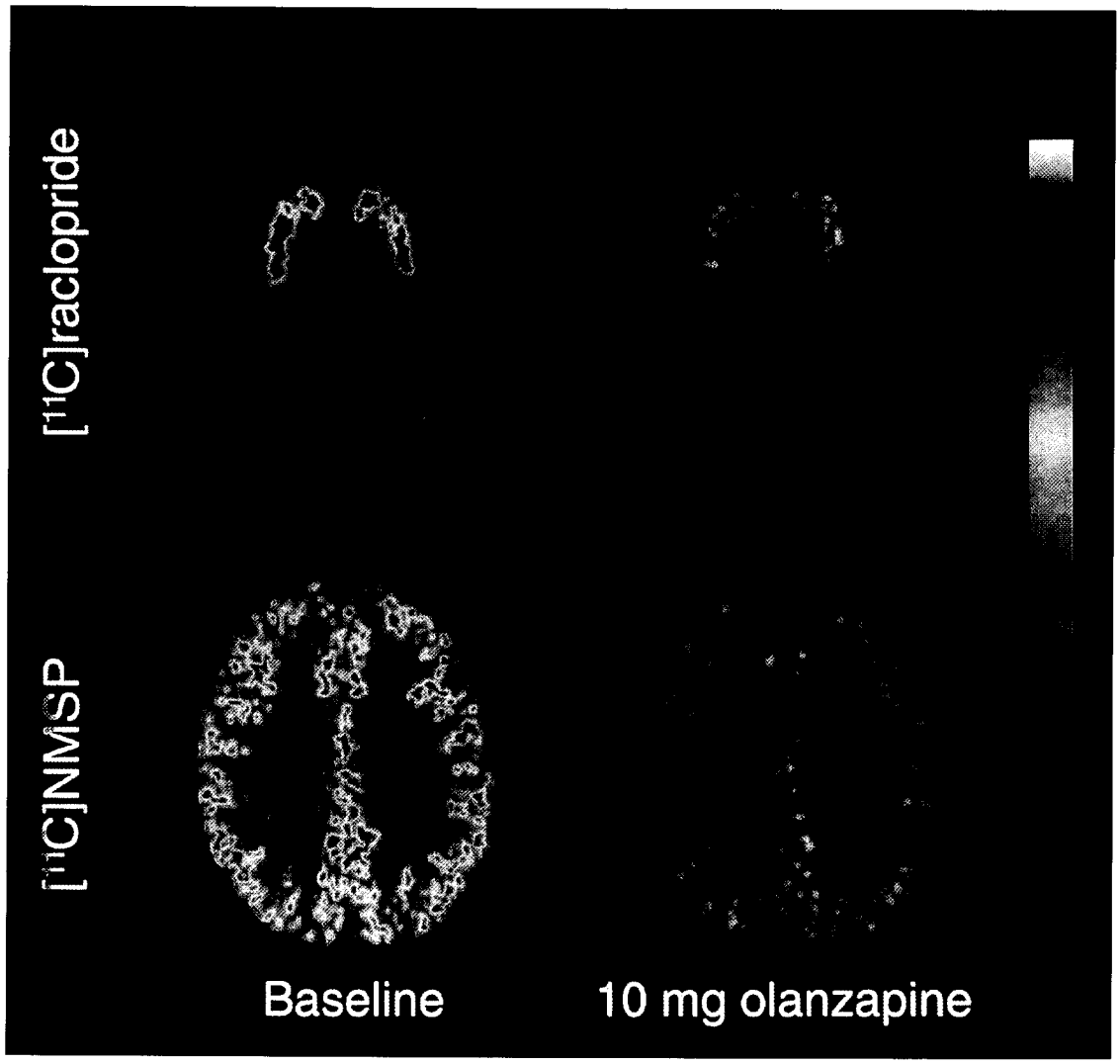

Figure 2. PET images showing the distribution of radioligand in horizontal sections of the brain of a healthy man, before (left) and after (right) oral administration of 10 mg olanzapine. Top row: section through the striatum after i.v. injection of [^{11}C]raclopride. Bottom row: section in the nearest section above the striatum after i.v. injection of [^{11}C]NMSP.

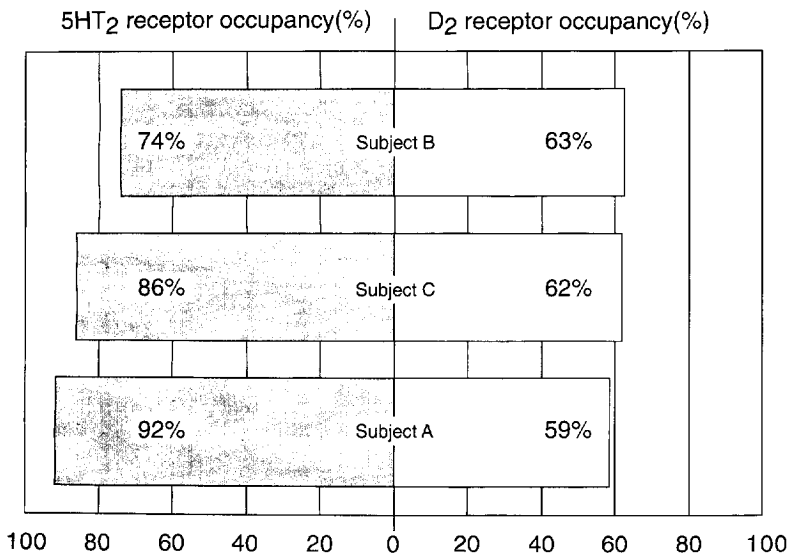

Figure 3. Calculated 5-HT$_2$ and D$_2$ receptor occupancy in three healthy subjects after a single oral dose of 10 mg olanzapine.

Consequently, the measured plasma concentrations can be used as anchor points to calculate receptor occupancy at various concentrations (Karlsson et al. 1995). The calculation assumes a linear relationship between drug concentration in brain and plasma and linear pharmacokinetics. During continuous treatment with daily dosing, a suggested half-life of olanzapine about 29 h (Nyhart et al. 1995) would give a C_{max} twice as high at steady-state as after a single dose. Thus, if the concentrations at 7 hours were doubled, D_2 receptor occupancy would be about 75%.

We have recently shown a statistically significant relation between antipsychotic effect and D_2 receptor occupancy in a controlled clinical study using raclopride as an antipsychotic (Nordström et al. 1993). On the basis of these and previous findings we have suggested that for classical antipsychotics there is a threshold for antipsychotic effect at about 70% D_2 receptor occupancy (Nyberg et al. 1995).

Several new compounds with *in vitro* affinity for both D_2 and 5-HT_2 receptors have been synthesized and are either under investigation or are already marketed as antipsychotic medication (Gerlach 1991; Meltzer 1991; Lieberman 1994). Using PET we have shown that risperidone, the first clinically available combined 5-HT_2 and D_2 receptor antagonist, induced an about 60% 5-HT_2 receptor occupancy and an about 50% D_2 receptor occupancy in healthy subjects after a 1 mg single oral dose (Nyberg et al. 1993). We are presently conducting a PET study in schizophrenic patients treated with risperidone at the suggested (Marder and Meilbach 1994) optimal dose 6 mg daily. A preliminary analysis of the first four patients indicates a D_2 receptor occupancy of 75–80%, and an even higher 5-HT_2 receptor occupancy (Farde et al. 1995). Thus, during clinical treatment with risperidone D_2 receptor occupancy is of the same magnitude as that induced by treatment with classical neuroleptics.

In a recent controlled double blind trial of olanzapine, clinical efficacy was demonstrated in the dose range 5 to 15 mg per day (Beasley et al. 1995). Extrapolation of our present single-dose observations suggests, that at the lower end of the clinically examined dose range the D_2 and 5-HT_2 receptor occupancy should be similar to that induced by standard doses of clozapine. At the higher end of the dose range, the D_2 receptor occupancy should be of the same magnitude as that induced by treatment with classical neuroleptics. Thus, detailed clinical evaluation of the dose-response characteristics of olanzapine, as well as direct clinical comparison to clozapine will provide valuable leads to the clarification of atypical antipsychotic drug action.

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