D_2 Dopamine Receptor Occupancy During Low-Dose Treatment With Haloperidol Decanoate

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Objective: The aim of this study was to examine the relationships among clinical effects, central D_2 dopamine receptor occupancy, and plasma concentrations of haloperidol in eight clinically stabilized schizophrenic outpatients who were responding to treatment with low doses of haloperidol decanoate. Method: During a 4-week interval of haloperidol decanoate dosage (dose range=30–50 mg), the patients' D_2 receptor occupancy was determined with positron emission tomography on two occasions. Plasma concentrations of haloperidol were determined with a sensitive high-performance liquid chromatography method. Results: One week after injection of haloperidol decanoate, the mean D_2 receptor occupancy was 73% (range=60%–82%), and the mean plasma concentration of haloperidol was 4.6 nmol/liter (range=2.9–9.7). After 4 weeks, the mean D_2 receptor occupancy had decreased to 52% (range=20%–74%), and the mean haloperidol concentration to 2.3 nmol/liter (range=1.0–4.4). Conclusions: The D_2 receptor occupancy 1 week after injection was high and comparable to that previously found in patients responding to acute treatment with classic neuroleptics. Prevention of relapse was maintained despite low D_2 receptor occupancy during the latter part of the treatment interval. These observations indicate that continuously high D_2 receptor occupancy may not be necessary to prevent schizophrenic relapses. The results emphasize the need for systematic clinical evaluation of intermittent low-dose treatment strategies.
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The efficacy of neuroleptic drugs in the treatment of schizophrenia is well established (1). In maintenance treatment, the drugs prevent psychotic relapses and influence long-term outcome favorably (2). However, there are several clinically important side effects of antipsychotic drug treatment, notably extrapyramidal symptoms (3, 4), cognitive impairment, akinesia, and dysphoria (5). The risk of side effects is often dose-related. Thus, for optimal clinical treatment it is essential to establish the minimal effective dose level. It has been reported that depot preparations of neuroleptics increase compliance with medication regimens (6). Clinical studies have indicated that low-dose depot medication may improve psychosocial functioning and reduce side effects (7). Such observations call for a systematic exploration of low-dose treatment with currently used antipsychotic drugs.

It is generally agreed that the antipsychotic effect of classic neuroleptics is induced by blockade of D_2 dopamine receptors (8, 9). This hypothesis has been supported by the consistent positron emission tomogra-

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TABLE 1. Characteristics of Eight Patients and Their Treatment With Haloperidol Decanoate in a 12-Week Study

Patient	Schizophrenia Subtype	Age (years)	Sex	Duration of Illness (years)	Months Since Last Hospital Discharge	Haloperidol Decanoate		Total Score at Inclusion in Study		Total Score at Endpoint of Study		CYP2D6 Genotype[a]
						Dose (mg/4 weeks)	Months Taking Same Dose	BPRS	CGI	BPRS	CGI	
1	Undifferentiated	42	F	3	28	30	9	24	2	21	2	Wild type/ wild type
2	Paranoid	46	M	11	131	30	7	22	3	24	3	Wild type/ wild type
3	Undifferentiated	33	M	5	22	40	9	28	2	24	2	Wild type/ wild type
4	Paranoid	36	M	8	13	50	13	26	3	28	3	Wild type/ wild type
5	Undifferentiated	37	M	14	15	50	8	33	3	24	3	Wild type/ wild type
6	Undifferentiated	29	M	3	40	30	5	20	2	20	2	B/wild type
7	Undifferentiated	30	M	4	8	50	7	24	2	21	2	Wild type/ wild type
8	Disorganized	33	M	5	107	50	15	34	4	35	4	B/B

[a]The B/B genotype is a poor metabolizer of haloperidol by the hepatic enzyme CYP2D6; the others are extensive metabolizers.

phy (PET) findings of high D_2 receptor occupancy in patients treated with antipsychotic drugs (10–12). It is interesting that extrapyramidal symptoms have been registered mainly in patients with occupancy above 80% (13), and a significant relationship between degree of D_2 receptor occupancy and occurrence of extrapyramidal symptoms has been demonstrated (14). On the basis of these findings, we have suggested that central D_2 receptor occupancy is a useful measure to establish guidelines for optimal clinical antipsychotic drug treatment.

D_2 receptor occupancy has not previously been examined systematically in patients treated with depot neuroleptics. Of particular interest is the determination of variations in occupancy during a dosage interval. The aim of this study was to examine the relationships among clinical effects, central D_2 receptor occupancy, and plasma concentrations of haloperidol in clinically stabilized schizophrenic outpatients responding to treatment with low doses of haloperidol decanoate.

METHOD

The study was approved by the Ethics Committee and the Radiation Safety Committee of the Karolinska Hospital, Stockholm. The patients were recruited from a specialized outpatient clinic for schizophrenic patients at the Karolinska Hospital and gave their informed consent. All clinical examinations and interviews for ratings of each patient were performed by the same investigator. Normative training rating sessions were held regularly throughout the study. PET examinations were performed at the Department of Clinical Neuroscience at the Karolinska Hospital. Plasma concentrations of haloperidol and CYP2D6 genotypes were analyzed at the Division of Clinical Pharmacology at Huddinge Hospital.

This was an open, exploratory study of eight schizophrenic patients receiving haloperidol treatment with depot injections every 4 weeks. The patients were monitored with clinical ratings for 12 weeks. PET examinations were performed after 9 and 12 weeks, i.e., 1 and 4 weeks after the last depot injection in the 12-week period. During the whole study the clinical ratings were done without knowledge of the patients' D_2 receptor occupancy and plasma concentrations of haloperidol. After the second PET examination, treatment was continued with unchanged doses for four patients, and treatment was discontinued for the other four. There was a 1-year clinical follow-up of both groups.

Characteristics of the patients and their treatment are summarized in table 1. Diagnoses according to DSM-III-R were made on the basis of a flexible clinical interview and review of chart records. The patients had to be responders to neuroleptic treatment and in stable clinical remission, which was operationally defined as having a maximum score of 36 on the Brief Psychiatric Rating Scale (BPRS) (15) for schizophrenia (Kolakowska's version: 18 items, rating scale of 1–7; 1=not present, 7=maximal), a maximum score of 4 (moderately ill) on the Clinical Global Impression (CGI) (16), and a minimum period of 6 months since the last hospital discharge.

The patients did not have any alcohol or substance abuse disorder, organic brain disorder (DSM-III-R), or other physical illness. Toxicological screening analyses of urine for benzodiazepines, opiates, amphetamine, cocaine, and cannabis were performed, with negative results, at the time of the patients' inclusion in the study and at the time of the PET examinations. Blood screening included standard tests of liver enzymes and electrolytes. Electrophoresis of blood proteins showed no abnormalities at the time of the PET examinations. Each patient's capacity to metabolize haloperidol in the liver by the polymorphic cytochrome P450 isoenzyme debrisoquine hydroxylase (CYP2D6) was determined by analysis of the CYP2D6 genotype (table 1).

At inclusion in the study, the patients had been treated only with haloperidol decanoate, 50 mg/ml, for at least 5 months, with no change of dose within the last 3 months. The dose range was 30–50 mg every 4 weeks (table 1). Before inclusion in the study, the patients' doses had been titrated so that side effects were minimal or absent, in accordance with local clinical practice. Doses had been adjusted after examination of the patients for signs and symptoms of extrapyramidal side effects at the time of the scheduled injections and asking, "Have you experienced any adverse events since the last injection?" Then, specific questions about extrapyramidal symptoms were asked. If extrapyramidal symptoms had been reported as intolerable by the patient, or if the clinical examination had revealed signs of "clinically significant" extrapyramidal symptoms, the injection dose had been reduced in steps of 5 mg. Treatment with haloperidol alone was ensured by requesting the patients to deposit previously prescribed drugs at the outpatient ward during the study. No anticholinergics were administered. Patient 8 was continuously treated with diazepam, 2 mg b.i.d., for episodes of anxiety.

Patients were included in the study on the occasion of a scheduled

depot injection at –8 weeks. Psychopathology was assessed with the BPRS and the CGI at inclusion in the study and at weeks –4, 0, 1, and 4. Extrapyramidal symptoms were assessed with the Simpson-Angus Scale (17), the Extrapyramidal Symptom Rating Scale (18), and a rating scale for drug-induced akathisia (19). Ratings of extrapyramidal symptoms were performed at weeks –8, –4, and 0; then daily for 11 days; then 13, 18, 23, and 28 days after the third depot injection.

The two PET examinations were performed 9 and 12 weeks after patients were included in the study (study weeks 1 and 4), i.e., 7 and 28 days after the last depot injection. The PET examinations were thus performed at the predicted time of maximal plasma concentration of haloperidol (mean=6.3 days, SD=3.5) (20) and immediately before the next scheduled injection.

After completion of the 12-week study, all patients continued their regular visits to the outpatient clinic. Psychopathology and side effects were rated and documented within the clinical monitoring program. Patients 3, 5, 6, and 7 continued their regular depot injections, whereas treatment was discontinued for patients 1, 2, 4, and 8. Reasons for discontinuation were that the patient had been well for a long time and had requested a trial period without medication and that there were no clinically identifiable risk factors for early relapse.

Blood samples (20 ml) for the determination of plasma concentrations of haloperidol were collected at weeks –8, –4, and 0. From study week 0, samples were drawn daily for 11 days, then 13, 18, 23, and 28 days after the depot injection. The samples were drawn into heparin-treated glass tubes and centrifuged. Plasma was frozen at –20 °C until analyzed. Haloperidol plasma concentrations were analyzed by high-performance liquid chromatography, as previously described (21), with minor modifications. The mobile phase consisted of 35% acetonitrile in aqueous 10-mM potassium phosphate (pH=7.0) and 1-mM *N,N*-dimethyloctylamine.

Leukocyte DNA was isolated from 10-ml venous blood samples by a guanidinium isothiocyanate method. To determine the genotype for the P450 enzyme CYP2D6, the mutated alleles CYP2D6A and CYP2D6B were identified by polymerase chain-reaction-based amplification of genomic DNA with allele-specific primers (22).

PET examinations were performed using the radioligand [^{11}C]-raclopride. After injection of [^{11}C]raclopride with high specific radioactivity, radioactivity in brain tissue was measured for 51 minutes with a Scanditronix PC2048-15B PET camera system with 4.5-mm resolution. A head fixation device was used to reproduce the same head position for each patient. Details of the examination procedure have been reported elsewhere (14, 23).

For the calculation of D_2 receptor occupancy, an equilibrium analysis was applied (23). The calculation was based on the ratio between the total radioactivity in the putamen and the total radioactivity in the cerebellum, which was used as the reference region. D_2 receptor occupancy was defined as the percent reduction in the putamen-cerebellum ratio during haloperidol treatment as compared to the ratio of 3.77 (SD=0.57) previously obtained in 34 healthy subjects (age=18–50 years) (24, 25). All control data were generated with the use of the same PET camera system and analytical approaches.

According to the law of mass action, the relation between receptor binding and the concentration of ligand at equilibrium is described by the hyperbolic (curvilinear) function $B=B_{max}*F/K_d+F$ (equation 1), where B_{max} is the number of available receptors, B is the concentration of ligand bound to receptors, K_d is the equilibrium dissociation constant, and F is the concentration of unbound ligand (23). Assuming a linear relation between ligand (haloperidol) in brain and plasma, and linear pharmacokinetics of the ligand, the plasma concentration of ligand may be substituted for F. In the present analysis D_2 receptor occupancy was plotted against plasma concentrations of haloperidol. Each data point was treated as a separate observation. Equation 1 was fitted, in a least squares design through an iterative procedure, to the 16 data points with the use of the Kaleidagraph 3.0 program (Abelbeck Software).

RESULTS

All eight patients completed the 12 weeks of the study according to schedule, including the PET examinations, clinical ratings, and blood samples. Clinical follow-ups were done for 1 year for seven patients and for 2 months for patient 5.

All eight patients had a low degree of overt psychopathology, as was required by the inclusion criteria. The psychopathology ratings (BPRS total scores) were stable throughout the study. The maximal increase in BPRS total score from week 0 to week 12 was 2 points (patients 2 and 4), while the maximal decrease was 9 points (patient 5). There were no statistically significant changes in BPRS scores during the study ($F=1.86$, $df=4, 28$, $p=0.14$, repeated measures analysis of variance). Seven patients were characterized as borderline mentally ill (2 points) or mildly mentally ill (3 points) by the CGI. Patient 8 was rated as moderately ill (4 points). Each patient's CGI scores were the same at inclusion in the study and at week 12.

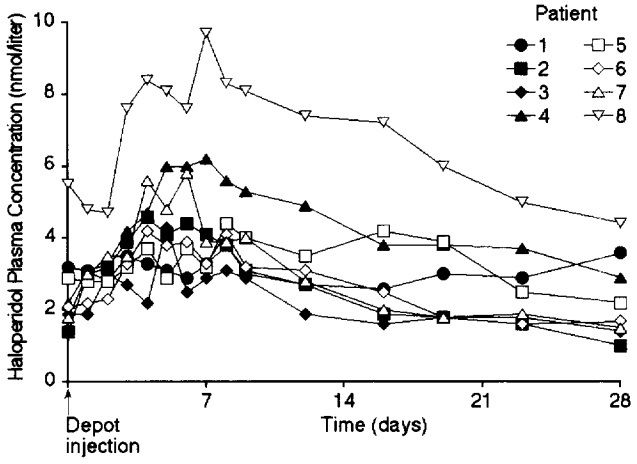
Before the study began, the doses of haloperidol decanoate had been titrated clinically to minimize extrapyramidal symptoms, and the degree of extrapyramidal symptoms was accordingly low in all patients. Parkinsonism was absent during the whole study for five patients (Extrapyramidal Symptom Rating Scale global score, range=0–8; 0=absent, 8=extremely severe) and borderline (score=1) to mild (score=3) for patients 1, 4, and 8. For six patients (patients 2–7), the total score on the Simpson-Angus rating scale for extrapyramidal symptoms (10 items, range=0–4; 0=none, 4=maximal) was never higher than 1. For patients 1 and 8, the score varied between 1 and 6. For these two patients, both rating scales for parkinsonism yielded slightly higher scores around the time of the maximal concentration of haloperidol than at the time of the minimal concentration. Patient 8 had the highest parkinsonism total scores throughout the study.

Akathisia was not present at any time in six patients, as assessed by the global item score on the Barnes akathisia rating scale (range=0–5; 0=absent, 5=severe). Patients 3 and 7 had mild akathisia at the time of the first PET examination. Dyskinesia was absent in five patients and borderline to mild in patients 2, 5, and 6, as assessed by the global item score on the Extrapyramidal Symptom Rating Scale (range=1–8; 0=absent, 8=extremely severe).

During follow-up, for four patients (numbers 3, 5, 6, and 7), treatment was continued with unchanged doses. Patients 3, 6, and 7 were in stable clinical condition and had no psychotic relapses during the year following the study. BPRS and CGI scores at follow-up 15 months after the study began (12 months after the second PET examination) did not exceed those at the beginning of the study. Patient 5 drowned, probably by accident, shortly after his last visit 2 months after the study.

For four patients (1, 2, 4, and 8), treatment was discontinued after week 12. In three of these four patients, psychotic symptoms recurred during the follow-up year. Patient 2 deteriorated within 4 weeks after the scheduled injection. Treatment was resumed, and he recovered clinically within 2 weeks. At the 1-year follow-up his BPRS scores were lower than they were when he

FIGURE 1. Plasma Concentrations of Haloperidol in Eight Schizophrenic Patients During a 28-Day Study (Weeks 0–4)[a]



[a]Haloperidol decanoate was administered on day 0.

began the study. Patients 1 and 4 had severe relapses with pronounced psychotic symptoms after 11 and 13 months, respectively. Both were hospitalized, and after resuming treatment they recovered within 3 weeks. Patient 8 has been monitored for 20 months at this writing and has not relapsed.

Patient 8 was homozygous for the mutated CYP2D6B allele, as determined by allele-specific amplification, and was thus a poor metabolizer of debrisoquine hydroxylase (table 1). The other patients were homozygous for the nonmutated "wild type" allele or heterozygous for the CYP2D6B allele and thus were genotypically extensive metabolizers (table 1).

Plasma concentrations of haloperidol were measured during 12 weeks. Individual data were plotted against time (figure 1). The mean trough value (samples taken at –8, –4, 0, and 4 weeks) was 2.5 nmol/liter (range= 1.0–5.5). At week 4, the time of the second PET examination, the mean concentration was 2.3 nmol/liter (range= 1.0–4.4). Maximal concentrations were measured 4–8 days after injection. At week 1, the time of the first PET examination 7 days after injection, the mean concentration of haloperidol was 4.6 nmol/liter (range= 2.9–9.7). Patient 8, who was a poor metabolizer of debrisoquine, had the highest concentration of haloperidol throughout. When all doses were normalized to 50 mg every 4 weeks, the mean calculated area under the plasma concentration curve during weeks 0–4 was 116 (range=74–183).

Images representing a transverse section of the brain at the level of the basal ganglia were reconstructed for visualization of [^{11}C]raclopride distribution (figure 2). The mean D_2 receptor occupancy was 73% (range=60%–82%) 1 week after injection and 52% (range=20%–74%) 4 weeks after injection. The difference in D_2 receptor occupancy between week 1 and week 4 was statistically significant (t=4, df=7, p=0.003, paired two-tailed test). D_2 receptor occupancy was plotted against the corresponding plasma concentrations of haloperidol, and equation 1 was fitted to the 16 data points (R=0.71) (figure 3).

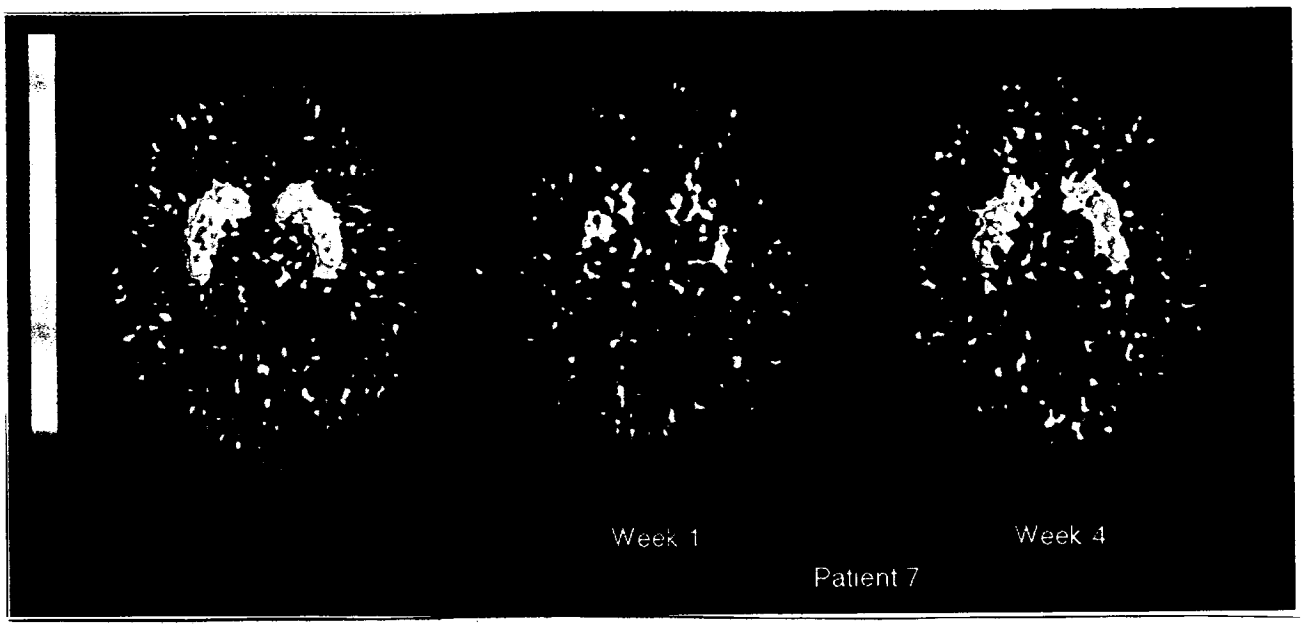
DISCUSSION

Eight schizophrenic outpatients in stable clinical remission were examined by PET during treatment with low doses of haloperidol decanoate (30–50 mg every 4 weeks). One week after injection the mean D_2 receptor occupancy was 73% (range=60%–82%), which is the same as the level previously found in patients responding to acute treatment (14). After 4 weeks, immediately before the next scheduled depot injection, the mean D_2 receptor occupancy had decreased to 52% (range=20%–74%), which is clearly lower than that found in patients responding to acute treatment with low to moderate doses of all currently used chemical classes of classic neuroleptics (13). Prevention of relapse was successfully maintained in our study patients despite low D_2 receptor occupancy during the latter part of the treatment interval.

The patients in this study were selected on the basis of their favorable response to treatment. They were in clinical remission, as indicated by low and stable psychopathology ratings and a period of at least 8 months since the last hospital discharge. The number of patients in the study is too small to permit conclusive evaluation of the general applicability of the low-dose treatment strategy we used. In general, patients do not relapse for weeks to months, even when medication is completely withdrawn. This delay is analogous to the slow onset of antipsychotic effect in acute treatment, although high D_2 dopamine receptor occupancy is achieved within hours after the first dose (26). We did not expect patients to relapse during one dosage interval, and this was the reason for the long observation before the PET examinations and the 1-year follow-up. To examine further whether there was a specific benefit of their treatment, four patients had their treatment withdrawn. Psychotic relapses followed in three of these four patients. By contrast, none of the patients who continued treatment relapsed within the year following the second PET examination. These observations support the view that the low doses we used were indeed effective in preventing psychotic relapses. Our present results challenge the conception that continuously high D_2 receptor occupancy, as a function of continuous dosage, is required to prevent schizophrenic relapses. We suggest that intermittent D_2 receptor occupancy over a long time might be sufficient for this purpose. The results emphasize the need for further systematic clinical evaluation of intermittent low-dose treatment strategies.

Several previous studies have approached a related issue by comparing continuous treatment to targeted intermittent treatment (27, 28). In the latter strategy, pharmacological treatment is started when early signs of psychotic relapse are identified. In this present study

FIGURE 2. Reconstructed PET Images Representing a Transverse Section of the Brain at the Level of the Basal Ganglia in a Healthy Subject (Left) and in a Schizophrenic Patient (Study Patient 7) 1 Week After Injection (Middle) and 4 Weeks After Injection (Right) of 50 mg of Haloperidol Decanoate

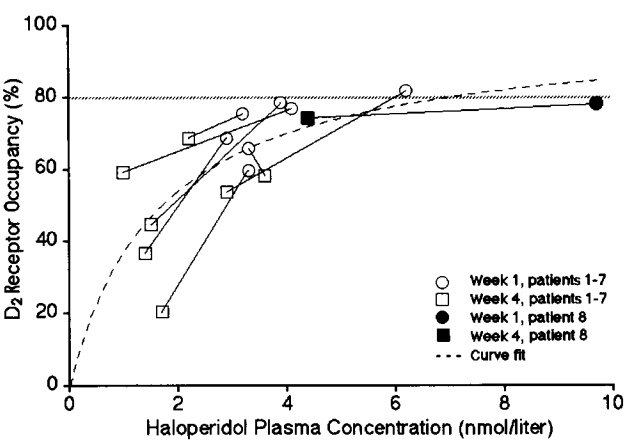


of patients treated with a depot drug, central D_2 receptor occupancy can rather be viewed as intermittent but at regular intervals. If intermittent high D_2 receptor occupancy is sufficient to prevent psychotic relapses, the question arises as to how frequently this peak occupancy is required. A possible treatment strategy could be to administer oral antipsychotics intermittently but on a scheduled basis. Our present findings call for exploration of such new treatment strategies.

D_2 receptor occupancy was plotted against plasma concentrations of haloperidol, and the curvilinear function of equation 1 could be well fitted to the data (R=0.71) (figure 3). Such a curvilinear relation has previously been shown for sulpiride (13), for haloperidol (29), and for raclopride when used as an antipsychotic (30). Haloperidol's high potency is indicated by the observation that even at plasma concentrations as low as about 4 nmol/liter, D_2 receptor occupancy was about 75%. Normalization of the plasma concentrations at a dose of 100 mg/month gave a mean trough value of 6.2 nmol/liter. A similar normalized trough concentration, 9.4 nmol/liter, was reported in a larger pharmacokinetic study with haloperidol decanoate (31). With a conversion factor of 10–20 from daily oral dose to monthly depot dose (32), the doses used in this study correspond to a calculated daily oral dose range of 1.5–5 mg. The minimal effective dose of haloperidol has not been defined in a dose-finding study. However, it is noteworthy that the doses we used are comparable with the oral dose range previously used to define the neuroleptic threshold for haloperidol (mean=3.7 mg/day, SD=2.3) (33).

Our clinical dosage strategies are based on our previous suggestion of an extrapyramidal symptom threshold at about 80% D_2 receptor occupancy (14). The presence of extrapyramidal symptoms is used as a tentative indicator of a too-high dose. Accordingly, optimal antipsychotic treatment with low extrapyramidal symptoms was the aim for the clinical dose titration of haloperidol decanoate before patients were included in the study. Extrapyramidal symptoms were absent or very mild in all patients. During the study, D_2 receptor occupancy was mostly lower than 80%. Our findings further support the view that in optimal antipsychotic

FIGURE 3. D_2 Receptor Occupancy Plotted Against Plasma Concentrations of Haloperidol in Schizophrenic Patients 1–7 (Extensive Metabolizer Genotype) and Patient 8 (Poor Metabolizer Genotype) 1 Week and 4 Weeks After Injection of Haloperidol Decanoate[a]



[a]Curve fit is discussed in the Method section. A tentative extrapyramidal symptom threshold (14) is indicated at 80% occupancy.

drug treatment of schizophrenia, extrapyramidal symptoms can be avoided while antipsychotic efficacy is maintained at a D_2 receptor occupancy level below 80%. The threshold that intermittently, or continuously, has to be surpassed to induce antipsychotic effect remains to be identified.

Plasma concentrations of neuroleptics vary among patients treated with the same dose (34). In some patients this pronounced variation corresponds to a variation in the rate of metabolism. Several neuroleptics, including haloperidol, are metabolized in the liver by debrisoquine hydroxylase (CYP2D6) (35). Poor metabolizers of debrisoquine, as compared to extensive metabolizers, develop higher plasma concentrations of haloperidol when given the same dose (21); they may thus be more susceptible to side effects of haloperidol and to developing higher D_2 receptor occupancy. The poor metabolizer of debrisoquine, patient 8, who had the highest parkinsonism scores, had the highest plasma concentration of haloperidol and high D_2 receptor occupancy in both PET examinations. This is the first experimental study in which the relation of the predicted propagation of CYP2D6 genotype to plasma haloperidol concentration, D_2 receptor occupancy, and risk of extrapyramidal symptoms has been demonstrated.

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