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In Vivo Assay for Neuroleptic Receptor Binding in the Striatum
Positron Tomography in Humans*

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Using PET, we investigated the potency in six patients of therapeutic doses of neuroleptic drugs for preventing specific binding of trace doses of intravenously administered ^{76}Br-labelled bromospiperone to corpus striatum *in vivo*. Measured receptor occupancy showed a clear-cut dose-dependent saturation curve with increasing daily oral dose of neuroleptics, indicating the validity and reliability of the method when used as an *in vivo* radioreceptor assay. Following drug withdrawal in eight patients, recovery to normal or supranormal receptor availability occurred in a matter of days. The results demonstrate an approach that may help resolve controversies about, and design better strategies for, neuroleptic treatment schedules.

Neuroleptic drugs are effective in controlling acute episodes of schizophrenia. However, the relationships between dosage and clinical response remain unclear (Davis *et al*, 1983; Curry, 1985), and the indications of maintenance therapy are a matter of debate (Hershon *et al*, 1972; Heinrichs & Carpenter, 1985; Gaebel & Pietzcker, 1985). These uncertainties may be due to insufficient information regarding the access of neuroleptics to, and rate of elimination from, target structures in brain.

The reliability of neuroleptic plasma levels has been questioned because they are not consistently correlated with antipsychotic effects, although radioreceptor assay, which takes into account the active metabolites, has occasionally provided better correlations (Creese & Snyder, 1977; Dahl, 1982; Meltzer *et al*, 1983; Rivera-Calimlim & Hershey, 1984). Neuroleptic drugs levels in brain tissue do correlate with behavioural effects in rats (Campbell *et al*, 1980), but this method is seldom applicable to humans.

Blockade of the central dopamine receptors is held to be the essential mechanism in the pharmacological action of the neuroleptics (Crow *et al*, 1976). Hence, to measure *in vivo* the actual occupation of brain dopamine receptors should provide an indirect estimate of the effective neuroleptic tissue levels, by analogy with the radioreceptor assay principle.

Positron emission tomography (PET) has recently emerged as a unique tool to investigate the striatal dopamine receptors in humans *in vivo* using radiolabelled high-affinity neuroleptics (Wagner *et al*, 1983; Baron *et al*, 1983; Leenders *et al*, 1984; Wong *et al*, 1984; Arnett *et al*, 1985; Maziere *et al*, 1985; Farde *et al*, 1985, 1986). Bromospiperone is a particularly suitable radioligand for this purpose, as shown by extensive validation studies in animals and humans (Kulmala *et al*, 1981; Crawley *et al*, 1983; Maziere *et al*, 1984, 1985; Baron *et al*, 1986). This approach should provide a semi-quantitative estimate of the neuroleptic binding sites available for interaction *in vivo* with the administered radioligand, and be ideally suited to evaluate the receptor occupancy rate both during and following oral treatment with neuroleptics.

Method

Patients

Ten patients (three women, seven men) were studied (Table I) after informed consent. Their age range was 21–82 years (mean 51.2). All had been on chronic medication with oral neuroleptics for more than 2 months. The clinical indications for neuroleptic treatment (Table I) were deliberately heterogeneous in order to ensure an as-wide-as-possible neuroleptic dosage range. Some patients were also receiving benzodiazepines, anticholinergic drugs or antidepressants at the time of the study, but none was on lithium. Four patients were studied twice, first on treatment, and then after withdrawal. In all, there were six studies of patients on treatment, and eight of patients off neuroleptics for periods of 1–12 days.

In order to allow comparison between the different studies, each neuroleptic medication was expressed as a weight-adjusted equivalent daily dose of chlorpromazine (CPZ). The calculation was based on established dose equivalence (Peroutka & Snyder, 1980). When this was

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TABLE I
Clinical data and results

Patient age and sex	*Clinical diagnosis*	*Neuroleptic treatment: mg/kg per day*	$(S/C)_{th}$[1]	*Studies on treatment*			*Studies after withdrawal*		
				CPZ eq. dose[2] *μmol/kg per day*	$(S/C)_m$[3]	P[4]	*Days stopped*	$(S/C)_m$[3]	P[4]
1. 62, M	Alzheimer's disease	Haloperidol (0.010)	1.86	1.4	1.81	93.7	—	—	—
2. 82, M	Senile dementia	Haloperidol (0.017)	1.69	2.4	1.64	92.2	—	—	—
3. 68, F	Chronic hallucinatory psychosis	Haloperidol (0.205)	1.81	—	—	—	1	1.90	111.6
4. 21, M	Schizophrenic disorder	Haloperidol (0.254) Levomepromazine (1.271)	2.21	94.3	1.33	27.3	3	1.87	71.9
5. 50, M	Syphilitic dementia	Haloperidol (0.042) Levomepromazine (0.174)	1.96	13.9	1.40	41.1	3	1.76	79.1
6. 43, F	Schizophrenia	Thioproperazine (1.429)	2.02	285.4	1.27	26.8	3	2.31	127.8
7. 72, F	Post-stroke agitation	Haloperidol (0.027)	1.78	—	—	—	7	1.59	76.3
8. 21, M	Schizophrenic disorder	Haloperidol (0.031)	2.21	4.4	1.65	53.6	7	2.17	96.9
9. 33, M	Alcoholism	Propericiazine (0.526)	2.11	—	—	—	10	2.15	103.6
10. 60, M	Vertigo	Thiethylperazine (0.375)	1.88	—	—	—	12	1.83	94.4

1. $(S/C)_{th}$ is the age-adjusted striatum/cerebellum theoretical ratio.
2. Neuroleptic daily dose expressed as chlorpromazine (CPZ) equivalent.
3. $(S/C)_m$ is the S/C ratio actually measured.
4. P is the percentage of unoccupied binding sites calculated from equation (4).

unavailable for a given neuroleptic, we calculated it from its inhibition constant (K_i) for ^{3}H-haloperidol binding *in vitro* (Leysen, 1984), since a very good correlation between the average clinical daily dose and the K_i for ^{3}H-haloperidol binding has been established (Creese *et al*, 1976; Seeman *et al*, 1976).

PET studies

The method used has been described elsewhere (Maziere *et al*, 1984, 1985; Baron *et al*, 1986). About 1.3 mCi of bromospiperone (BSP) labelled with ^{76}Br ($T_{½} = 16.2$ h) was injected i.v. as a bolus with a specific activity of 330 ± 100 mCi/μmol. The amount of bromospiperone injected was 2.75 ± 1.26 μg. From a whole-body kinetic biodistribution study performed in a baboon, it was shown that about 25% of the injected dose was concentrated in the liver. For a ^{76}Br-BSP study in man, the radiation dose absorbed by the liver has been estimated as 1.9 rad, which is lower than that of standard nuclear medicine procedures such as bone marrow or liver scans (Robertson, 1982; Maziere *et al*, 1985). Permission to carry out ^{76}Br-BSP studies was granted by the ethical committee of the Atomic Energy Commission.

PET studies were performed on the time-of-flight positron camera at the Laboratoire d'Electronique et de Technologie de l'Informatique, Grenoble. Spatial resolution in the plane of section is about 12 mm, slice thickness about 13 mm and undetected space between slices about 3 mm using the medium-resolution mode. Seven slices were acquired simultaneously, levels being chosen from a standard PET atlas (Inoue *et al*, 1985) so that the cerebellum was studied at the lower cut and the striatum at the third cut; 1 cm and 4 cm, respectively, above and parallel to the orbitomeatal plane. A ^{68}Ge-^{68}Ga transmission scan was performed for accurate attenuation correction. A 30-min scan was acquired, starting 4.5 h after injection.

From these images, the striatum and cerebellum radioactive concentrations were obtained by means of a standardised, previously validated method using regions of interest (ROIs) (Maziere *et al*, 1985; Baron *et al*, 1986). In the four patients on large doses of neuroleptics,

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TABLE II

^{76}Br-BSP relative radioactive concentrations (mean ± s.d.) showing no significant differences among subgroups for any variable

76 Br-BSP concentration	*Controls*	*On neuroleptics*	*Off neuroleptics*	*P*
Cerebellum,[1] $t=5$ min	1.36 ± 0.52 ($n=11$)	1.23 ± 0.55 ($n=6$)	1.19 ± 0.21 ($n=8$)	NS
Cerebellum,[1] $t=4.5$ h	1.41 ± 0.41 ($n=17$)	1.42 ± 0.27 ($n=6$)	1.42 ± 0.20 ($n=8$)	NS
Blood,[2] $t=5.0$ h	0.47 ± 0.19 ($n=17$)	0.50 ± 0.19 ($n=6$)	0.50 ± 0.12 ($n=8$)	NS

1. As percentage injected dose per litre of brain.
2. As percentage injected dose per kilogram of blood.

the striata could not be clearly depicted on the 4.5 h PET images because of receptor occupancy by neuroleptic treatment as shown and discussed below. Since these patients were also studied after drug withdrawal, the ROIs defined on the latter PET images were copied automatically on to the former by means of dedicated software. This was possible because of special care taken for reproducible positioning in these repeated PET studies by use of crossed laser beams projected on standardised bony landmarks.

Determination of the percentage of unoccupied binding sites

Since the cerebellum is virtually devoid of specific binding for neuroleptics (Luabeya *et al*, 1984; Martres *et al*, 1985), the difference between the ^{76}Br-BSP concentrations in the striatum and in the cerebellum represents the specifically bound ligand in the striatum (Kuhar *et al*, 1978). The fraction f of dopamine sites occupied by the neuroleptic medication can therefore be described by the following equation:

$$f = [(S_{th} - C) - (S_m - C)] / [S_{th} - C] \quad (1)$$

where C is the radioactive concentration in the cerebellum, S_{th} the theoretical (expected) radioactive concentration in the striatum and S_m that actually measured in the study of the patient. By dividing each term by C, equation (1) becomes

$$f = [(S/C)_{th} - (S/C)_m] / [(S/C)_{th} - 1] \quad (2)$$

where $(S/C)_{th} - (S/C)_m$ are the expected and the measured striatum-to-cerebellum radioactive concentration ratios, respectively.

The use of equations (1) and (2) relies on the assumption that the parameter C, which is measured at 4.5 h and represents both free ligand and non-specific binding, is unaffected by neuroleptic treatment.

The percentage of neuroleptic sites left unoccupied by the neuroleptic medication can be expressed as

$$\text{percentage of unoccupied sites} = 100\ (1 - f) \quad (3)$$

which can be rewritten as

$$\text{percentage of unoccupied sites} = 100\ \{[(S/C)_m - 1] / [(S/C)_{th} - 1]\} \quad (4)$$

Data analysis

From the radioactive concentration values measured in the striatum and the cerebellum, the $(S/C)_m$ ratio was calculated for each subject.

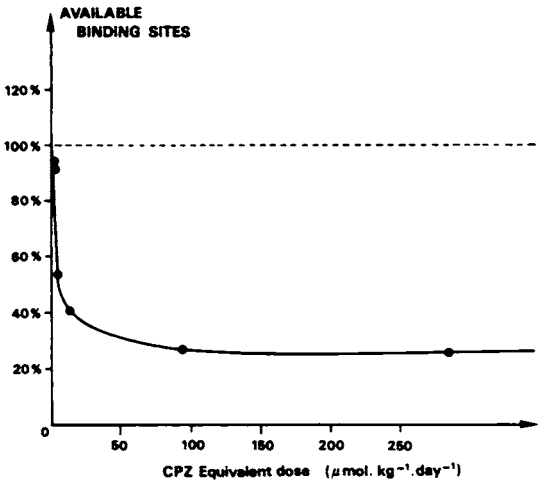

FIG. 1 Available binding sites (percentage of unoccupied neuroleptic sites) in the six ^{76}Br-BSP PET studies performed during neuroleptic treatment, plotted against the weight-adjusted neuroleptic daily dose expressed as chlorpromazine (CPZ) equivalent (CE). The data were best fitted by the bi-exponential line $P = 98 \exp(-0.3\ CE) + 34 \exp(-0.001\ CE)$.

To obtain the $(S/C)_{th}$ value, data from 17 control subjects studied by the same procedure were used. However, it was necessary to adjust for age according to the highly significant negative linear regression relating S/C and age found in controls (Baron *et al*, 1986). Finally, using $(S/C)_m$ and $(S/C)_{th}$, the percentage of unoccupied sites was determined according to equation (4).

Results

Blood and cerebellar values

There was no significant difference between patients and controls in early cerebellar tracer uptake, late blood tracer concentration, or 4.5 h cerebellar uptake (parameter C, see methods) (Table II).

Studies on neuroleptic treatment

For patients on neuroleptic treatment, we found a clear-cut dose-dependent decrease in the $(S/C)_m$ ratio, which ranged from 1.81 at lowest dosage to 1.27 at highest dosage (Table I).

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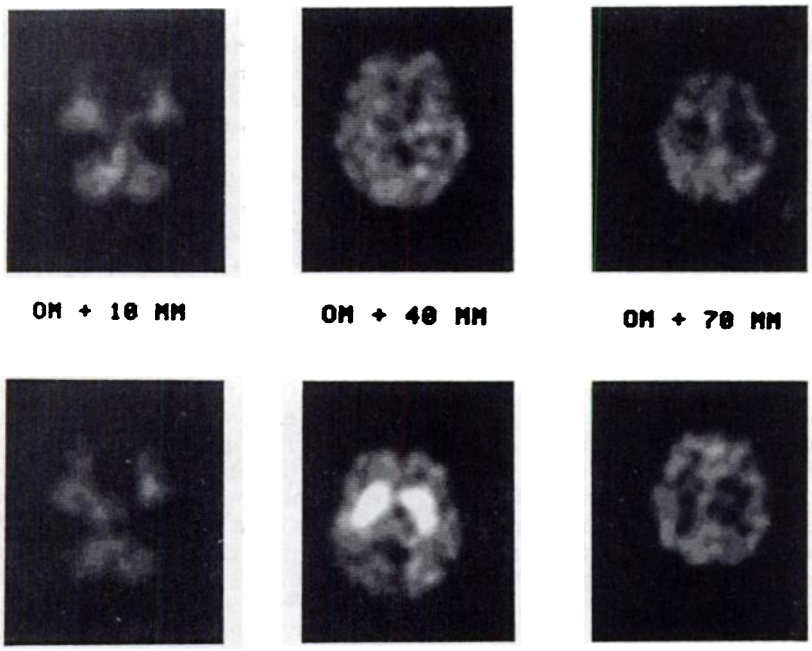

FIG. 2 ^{76}Br-BSP PET images (obtained at $t = 4.5$ h) at cerebellum level (orbitomeatal plane + 10 mm), basal ganglia level (OM + 40 mm), and corona radiata level (OM + 70 mm) in patient 6 both during high-dosage neuroleptic treatment (upper row) and one week later following 3 days of withdrawal (bottom row) (see Table I for details). These images strikingly depict the featureless pattern typically found during high-dosage treatment, indicating almost full receptor occupation by neuroleptics, and the rapid recovery of high radioactive uptake in the striatum, demonstrating in this patient a particularly fast neuroleptic washout from brain.

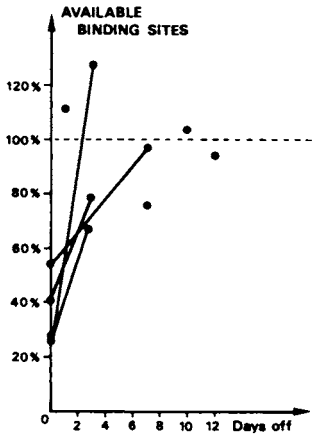

FIG. 3 Measures of available binding sites obtained in the eight studies performed after neuroleptic withdrawal, plotted against the number of days off. The lines join the values measured in four patients both during treatment and following withdrawal.

The percentage of unoccupied sites showed a striking dose-dependence (Fig. 1), and ranged from 93.7% to 26.8% for lowest and highest doses, respectively (Table I). The CPZ equivalent daily oral dose corresponding to 50% of unoccupied sites was about 6 μmol/kg (about 2 mg/kg).

Studies after neuroleptic withdrawal

Within days of withdrawal, there was a rapid trend for the $(S/C)_m$ ratio to return towards normal values (Table I). This was strikingly depicted in the four patients who were studied on both occasions, and particularly in the two patients on high neuroleptic doses, in whom the 4.5-h PET ^{76}Br-BSP image at basal ganglia level changed from a featureless pattern while on neuroleptics to the pattern of high striatal uptake typical of normal subjects 3 days only after withdrawal (Fig. 2).

When the results were expressed as the percentage of unoccupied sites (Fig. 3), it was observed that the majority of patients (6/8) fell into a somewhat curvilinear recovery

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line apparently crossing the 100% level by 7–12 days after withdrawal. However, the extent of recovery seemed to depend on both the withdrawal interval and the percentage of unoccupied sites during treatment; for the three repeated studies that followed this pattern, the mean percentage of recovery per day was 11.3% (range 6.2–14.9%). The last two patients (patients 3 and 6) were somewhat atypical in that both not only reached but even fell above the 100% level very early (112% and 128% one and three days after neuroleptic withdrawal, respectively), including patient 6, whose percentage of unoccupied sites during treatment was very low (27%).

Discussion

Our results are the first to show a dose-dependent occupation of human striatal binding sites by orally given neuroleptics in chronic schedule; there is no comparable data in the literature, although Meltzer *et al* (1977) found a positive linear correlation between prolactin plasma levels and oral dose of CPZ in humans up to 600 mg/day. Using ^{76}Br–BSP or other radioligands, several previous PET studies demonstrated total occupation of striatal neuroleptic binding sites by various binding sites by various neuroleptics in humans (Baron *et al*, 1983; Maziere *et al*, 1985; Farde *et al*, 1986), but none studied the full range of neuroleptic dosage and, in turn, of receptor occupancy.

The fact that despite very high doses of neuroleptics the striatum-to-cerebellum ratio did not fall to unity (Table I) may seem surprising, but it is consistent with previous results obtained in baboons loaded with unlabelled spiperone and in two human subjects administered haloperidol i.m. (10 mg) before PET study (Maziere *et al*, 1984, 1985). Errors in the estimation of occupancy rates because of competition between neuroleptics and labelled bromospiperone are unlikely, for the amount of radioligand administered was so small (5.8 ± 2.7 nmol) as theoretically to occupy less than 1% of the striatal receptors (Maziere *et al*, 1985). We believe that there was indeed full receptor occupation, but that the *S/C* ratio did not reach 1.0 because of higher non-specific uptake of bromospiperone in the striatum than in the cerebellum (Laduron *et al*, 1978; Barone *et al*, 1985), possibly a reflection of regional differences in, for example, ligand internalisation, neuronal–glial relative density, gray/white matter ratio or spirodecanone sites (Laduron, 1984; Dannies *et al*, 1984; Chugani *et al*, 1985).

Our data indicate that it should be possible to estimate the rate of striatal dopamine-receptor blockade from knowledge of the daily oral dose of neuroleptics. Although the antipsychotic effect of the neuroleptics may be more related to dopamine blockade in the mesolimbic system (Crow *et al*, 1976), there is little evidence to suggest that mesolimbic and striatal receptors respond differently to chronic neuroleptic treatment (Jenner & Marsden, 1983; Roth, 1983); unfortunately, present PET methods are not well suited to investigate this issue. From our work, however, one may infer the dose necessary to achieve full saturation of receptors, above which there may be no further therapeutic benefit, but increased risk of side-effects.

The studies performed after neuroleptic withdrawal showed return to 100% unoccupied sites within a few days (Figs 2 and 3), establishing that washout of neuroleptics from their striatal binding sites is a rapid process. Up till now, it was widely assumed that this washout was much slower, based on clinical, behavioural, and pharmacokinetic data (Hershon *et al*, 1972; Marsden *et al*, 1975; Byck, 1975; Korpi *et al*, 1984; Campbell *et al*, 1985). Our results, however, fully agree with reported neuroleptic clearance rates from plasma (Byck, 1975; Forsman & Ohman, 1977; Itoh *et al*, 1984) and brain tissue (Ohman *et al*, 1977), and with *in vivo* studies in rats (Saelens *et al*, 1980; Ferrero *et al*, 1983; Owen *et al*, 1983). Our findings may help in the design of improved treatment strategies. In addition, they strongly suggest that long-lasting remissions of psychotic patients following neuroleptic withdrawal are not due to persistent dopamine-receptor occupation. Other explanations must be sought, such as protracted neurochemical or cellular changes from neuroleptics (Benes *et al*, 1985), non-dopamine-blocking antipsychotic action of neuroleptics (Nishikawa *et al*, 1985), psychosocial therapy (Hogarty & Goldberg, 1973), or the spontaneous course of the mental illness with time (Davis *et al*, 1983).

In patients 3 and 6, the recovery rate was even faster, with levels above 100% being reached one and three days after neuroleptic withdrawal, respectively. These data presumably indicate dopamine-receptor supersensitivity (Jenner & Marsden, 1983). However, the intersubject variability in underlying mental disorder and in neuroleptic drug regimen may have affected these recovery rates, and will have to be controlled in the future.

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