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ORIGINAL INVESTIGATION

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In vivo characteristics of dopamine D_2 receptor occupancy by amisulpride in schizophrenia

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Abstract The relationship between the daily oral dose of the benzamide amisulpride and the striatal D_2-dopamine receptors occupancy was investigated in 11 schizophrenic patients using positron emission tomography with ^{76}Br-bromolisuride. The patients were studied before and during chronic treatment with amisulpride over a wide range of doses. The test-retest variability of the method was estimated to be 5.8% in a group of four patients receiving placebo. A curvilinear relationship was demonstrated between the amisulpride doses and the D_2-receptor occupancy. A range of 70–80% occupancy of the striatal D_2 receptors, suggested as an optimal interval for therapeutic action on positive psychotic symptoms, was obtained with doses of amisulpride ranging between 630 and 910 mg per day, while an occupancy of 85%, suggested to be associated with pronounced extrapyramidal side-effects, was reached with 1100 mg per day.

Key words Schizophrenia · PET · Neuroleptics · Dopamine receptors

Introduction

The dopamine D_2 receptor is considered to be one of the target sites of neuroleptic drugs because their in vitro affinity for D_2 receptor in animals correlates with their antipsychotic potency in humans (Creese 1976). Hence these drugs, given at usual doses, may exert their therapeutic action on positive symptoms of schizophrenia by decreasing the dopaminergic activity mediated by this receptor class.

However, the substituted benzamide derivatives such as amisulpride possess a peculiar dose-dependent behavioral profile, according to animal studies and clinical evidence. In animals, low doses of amisulpride facilitate dopamine-mediated behaviors (Puech et al. 1978; Carnoy et al. 1986; Guyon et al. 1993), and increase the in vivo release of dopamine in cerebral structures (Scatton et al. 1994), whereas at high doses, amisulpride shares with conventional neuroleptics their ability to antagonize dopamine receptor mediated effects of apomorphine (Scatton et al. 1995). In clinical situation, whereas usual doses (600–1200 mg/day; Costa e Silva 1989; Boyer et al. 1990; Delcker et al. 1990; Hillert et al. 1994) are effective in treating positive schizophrenic symptoms, a therapeutic effect of low doses (50–100 mg/day) of amisulpride on some primary deficit symptoms of schizophrenia has been reported recently (Paillère-Martinot et al. 1995). This last activating effect may be due to a dopaminergic facilitation via the blockade of presynaptic D_2 receptor, or via the blockade of D_3 receptors for which amisulpride has a high affinity (Sokoloff et al. 1990).

In an actual therapeutic situation, the chronic effect of low doses of neuroleptics on the extent of in vivo D_2 dopamine receptor blockade has not been investigated by longitudinal studies in schizophrenic patients. With usual doses of neuroleptics, the stabilization of productive psychotic symptoms was associated with an in vivo occupancy of the striatal D_2 receptors of at least 65%, in patients treated with various neuroleptics and studied with positron emission tomography (PET) (Farde et al. 1988).

Raclopride dosage has been shown to be generally related to D_2 receptor occupancy and to the degree of antipsychotic effect (Nordström et al. 1993). However, with conventional doses of other neuroleptics, identical levels of striatal D_2 receptor occupancy were reported in responder and nonresponder schizophrenics (Wolkin et al. 1989; Martinot et al. 1990). In other respects, extrapyramidal side-effects were more likely to occur when the striatal D_2 receptor occupancy reached 82±4% (Farde et

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al. 1992). On the whole, these studies suggest that the optimal D_2 occupancy interval associated with an antipsychotic effect is approximately between 70 and 80% (Farde et al. 1995).

These results underscore the need to investigate the dose – D_2 occupancy relationship of neuroleptic compounds in actual therapeutic situation. Other studies have shown a relationship between the chlorpromazine-equivalent dose of various oral neuroleptics and the PET-estimated D_2 receptor occupancies (Cambon et al. 1987; Baron et al. 1989). However, the validity of such estimates of equivalence for low doses of neuroleptics is unknown.

A common drawback of the in vivo receptor occupancy studies by brain imaging is the difficulty in assessing the baseline measure of D_2 receptor before treatment, which can vary extensively across individuals (up to 40%; Farde et al. 1988). In previous studies, theoretical baseline values were often only inferred from averaged data obtained in normal control subjects. Although useful when investigating usual doses of neuroleptics, these estimates of the baseline measure of the D_2 receptor may be imprecise for assessing low degrees of occupancy, such as those induced by treatment of negative schizophrenic symptoms with very low doses of some neuroleptics.

We previously reported a dependence of striatal D_2 receptor occupancy on neuroleptic dosages for various neuroleptics (Martinot 1990). We now extend those findings for a single compound, amisulpride, over a wide dose range. The correspondence between the levels of occupancy and the amisulpride dosage, was considered with respect to in vivo D_2-occupancy thresholds reported in the literature for antipsychotic (70–80%) and extrapyramidal side-effects (85%). Patients were studied prospectively: the in vivo baseline uptake of ^{76}Br-bromolisuride (Blis) was first measured with PET in untreated patients, and a second scan was performed in the same patients, while treated. In addition, the reproducibility of the PET assay with ^{76}Br-Blis was studied in some patients treated with placebo.

Subjects and methods

Patients and administered neuroleptic dosages

Within a week of their admission to the psychiatric departments of the Salpêtrière, Bicêtre, or Sainte-Anne hospitals, inpatients were assessed by psychiatrists (M.L.P.M., J.L.M., M.F.P.) from their respective departments, who observed and interviewed the patients, interviewed the patient's relatives, and, in most cases, the physician who referred the patients. Patients were included in the study if they were 18 years of age or over, fulfilled the DSM III-R criteria for schizophrenic disorder, and were in a drug-naive or neuroleptic-free condition for the past 4 months, without prior depot neuroleptic treatment. Informed consent was obtained in all cases. The ethics committee of the Commissariat à l'Energie Atomique approved the protocol of the study.

A total of 15 patients meeting these criteria participated in this study. Eleven were studied before and during amisulpride treatment, and four were studied before and during placebo treatment.

Among the 11 patients studied untreated and on neuroleptics, seven patients showed an initial symptomatology of prominent negative symptoms: SANS (Andreasen 1987) total score=86±11; and a weak score in positive symptoms: SAPS (Andreasen 1987) total score=14±10. There were five men and two women, with a mean±SD age of 22±3 years; six patients met the DSM-IIIR criteria for the disorganized type, and one for the undifferentiated type. An initial PET examination was performed before treatment. These patients were treated with a low (activating) daily dose of amisulpride (50 or 100 mg in the morning) for 3 weeks, after which they were re-scanned. These seven patients were taken from a larger double-blind therapeutic trial of low doses of amisulpride versus placebo (Paillère-Martinot et al. 1995), and had been receiving the active compound. In addition, in order to widen the range of doses studied, four schizophrenics, one female, three males, aged 27±8 years (two disorganised, one paranoid, one undifferentiated), were studied untreated and while having received, respectively, 200, 200, 500, and 800 mg/day of amisulpride, for at least 2 weeks. They had mixed positive and negative symptoms (SANS: 54±15, SAPS: 51±30).

Reproducibility study in placebo-treated patients

Four other patients, initially included in the double-blind trial amisulpride versus placebo, actually received placebo. They were two men and two women: two disorganized and two undifferentiated schizophrenics, aged 18±0.5 years. They had paired PET scanners, before and after 3 weeks on placebo.

PET methodology

Bromolisuride (Blis) labelled with bromine 76 (^{76}Br) (half-life=16.2 h) was used to study the central D_2 dopaminergic receptors. Preparation of the radioligand and description of the method have been published elsewhere (Mazière et al. 1986; 1990). Briefly, the PET studies were performed in the afternoon with the LETI TTV 01 time-of-flight positron camera which provides seven cerebral slices (inplane resolution=13 mm). Subjects' heads were positioned in the head-holder by means of a crossed laser beam system, so that the lowest slice (15 mm above and parallel to the orbito-meatal plane) included the cerebellar hemispheres, and the third slice (45 mm above the orbitomeatal plane) included the striata. Before radioligand injection, a Ge-68/Ga-68 transmission scan was collected for subsequent attenuation correction. After the radiotracer injection, an early image was obtained between 0 and 15 min. A second emission scan, lasting 30 min was collected 2 h after injection. Accurate repositioning of the patients' head during the second PET study was ensured by reference to measurements of the subjects' head position and position of the head holder during the first PET study, with regard to the crossed laser beams of the tomograph.

^{76}Br-Blis was injected intravenously as a slow bolus. the mean±SD amount of injected radioactivity, expressed in millicuries, was 1.08±0.30 in the untreated patients at the time of the first PET study, and 1.05±0.29 in the treated patients at the time of the second PET study (paired t=0.22, df=10, P=0.82).

The fraction of ^{76}Br-Blis specifically bound to the D_2 striatal receptord (specific binding) was estimated by the value of the striatum to cerebellum ratio obtained 2 h after injection of the radiotracer. The striatum-cerebellum radioactivity concentration ratio was taken as an index of the radioligand specific binding in the striatum which reflects the D_2 receptors available for binding in that structure (Mazière et al. 1985; Baron et al. 1986; Delforge et al. 1991).

A standardized protocol was used to measure cerebellar and striatal radioactive concentration from regions of interest (ROI) according to a method previously detailed (Martinot et al. 1990, 1991). The ROIs defined on the images of the first PET study were copied digitally onto the corresponding images of the second PET study.

Table 1 Individual PET ^{76}Br-bromolisuride results before and during chronic treatment by amisulpride. *LatCrb1*: radioactive concentration in the cerebellum (fraction of the injected dose×10^{-5}) on the late images (t=2 h after injection) before treatment. *S1*: radioactive concentration in the striata (fraction of the injected dose×10^{-5}) before treatment. *S/C1*: striatum to cerebellum ratio values before treatment. *Dose*: amisulpride dosage (mg/day). *LatCrb2*: radioactive concentration in the cerebellum (fraction of the injected dose×10^{-5}) on the late images (t=2 h after injection) during treatment. *S2*: radioactive concentration in the striata (fraction of the injected dose×10^{-5}) during treatment. *S/C2*: striatum to cerebellum ratio values during treatment. *% free*: percentage of available binding sites. *% Occup*: percentage of occupancy

N°	Age	LatCrb1	S1	S/C1	Dose	LatCrb2	S2	S/C2	% Free	% Occup
1	20	1.037	3.783	3.65	50	0.857	2.905	3.39	90.18	9.82
2	23	0.784	2.932	3.74	50	0.895	3.228	3.607	95.15	4.85
3	19	1.035	3.78	3.652	50	0.781	2.777	3.556	96.38	3.62
4	23	1.074	4.903	4.565	100	1.028	3.881	3.776	77.87	22.13
5	28	1.371	5.242	3.823	100	1.583	4.909	3.101	74.42	25.58
6	24	1.868	9.468	5.069	100	1.336	5.622	4.208	78.84	21.16
7	19	0.931	3.59	3.85	100	1.012	3.537	3.495	87.54	12.46
8	25	0.784	2.96	3.77	200	0.788	2.14	2.71	61.73	38.27
9	20	1.073	3.872	3.61	200	1.057	2.36	2.23	47.13	52.87
10	24	0.782	3.15	4.02	500	0.767	1.7	2.22	40.4	59.6
11	39	0.953	3.96	4.16	800	1.033	1.81	1.75	23.73	76.27

Results

Tracer accessibility and non-specific binding

Fifteen minutes after tracer injection, the mean±SD tracer concentrations measured in the cerebellum (expressed as fraction of the injected dose×10^{-5}) were 2.14±0.51 for the untreated patients, and 1.96±0.47 in the treated patients in the second PET examination (paired t-test=1.34, df=10, P=0.21). Two hours after injection, the mean tracer concentrations measured in the cerebellum were 1.06±0.31 in the untreated patients, and 1.01±0.25 when the patients were treated with amisulpride (paired t=0.82, df=10, P=0.43). These results indicate that the accessibility of the tracer to the cerebellum which is taken as an estimate of the non-specific binding, was comparable in all PET examinations.

Measurements of the relationship between the striatal D_2 receptor occupancy and the amisulpride dose

Specific binding, as measured by the striatum to cerebellum radioactivity concentration ratio (S/C ratio) decreased in patients undergoing amisulpride treatment (mean±SD=3.09±0.76) with respect to the untreated state (3.99±0.45; paired t=4.07, df=10, P=0.002), suggesting significant striatal D_2 occupancy by amisulpride.

The D_2 receptor occupancy by amisulpride was computed from the equation:

% occupancy=100–100 (X2–1/X1–1),

where X1 is the measured value of the S/C radioactivity concentration ratio from the first PET scanning, and X2 the S/C ratio from the second scanning (Baron 1989).

In the whole group, the D_2-amisulpride occupancy ranged from 4 to 76% (Table 1). The dose-occupancy relationship was fitted with an algorithm using a hyperbolic equation (Graphpad Prism software, 1994) which describes the binding of a ligand following the law of mass action. It is a non-linear fitting programme using an iterative approach for the minimisation of the sum of the squares. The adjustment of the variables is performed using the Levenberg-Marquardt algorithm. This yielded the dose-occupancy curve shown in Fig. 1.

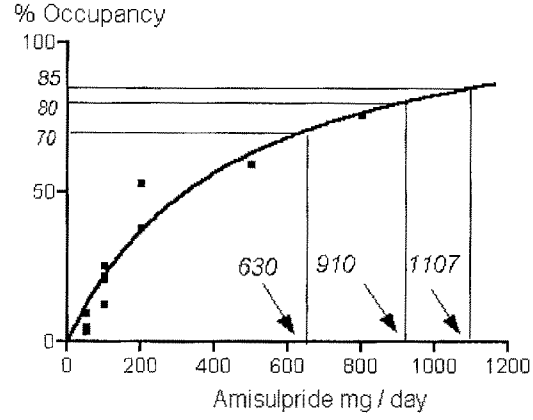

Fig. 1 Fitted curve between the striatal D_2 receptor occupancy and the daily dose of amisulpride. The *arrows* indicate the threshold values for optimal antipsychotic effect, and the value for pronounced extrapyramidal side effects

Table 2 Striatum to cerebellum ratios values in four placebo-treated patients

Pcb	S/C1	S/C2	Difference
1	4.267	4.638	–0.371
2	3.590	3.667	–0.077
3	3.856	4.476	–0.620
4	3.439	3.222	0.217

Reproducibility in the patients treated with placebo

The four patients in the placebo group were injected with 1.15±0.33 millicuries on the first scan, and 1.30±0.15 on

the second scanning (paired t=0.67, df=3, P=0.55). The S/C ratio was 3.78±0.36 at the initial scan, and 4.00±0.67, 3 weeks later (paired t=1.17, df=3, P=0.32; Table 2). The values of the striatum to cerebellum concentration ratios in the first study showed a significant correlation with those of the second study (r=0.92). This yields a group test-retest variabiality of 5.8%.

Discussion

PET with ^{76}Br-Blis was used to assess the striatal dopamine D_2 occupancy in 11 schizophrenics chronically treated by a wide range of amisulpride doses. Patients had been either neuroleptic-naive or neuroleptic-free for at least 4 months prior to initial treatment with amisulpride, making it highly unlikely that the baseline measurements of striatal D_2 receptor specific binding were biased by previous treatments (Kornhuber et al. 1989). Changes in D_2 receptor occupancy after amisulpride treatment were measured from this baseline by paired PET studies in the same patients, and not by comparison to theoretic estimates of D_2 receptor number from normal subjects, minimizing interindividual variability. The test-retest variability of the method was estimated to be 5% for a group of four patients scanned twice without active neuroleptic treatment, allowing estimation of occupancy during low dose treatments.

Pharmacokinetic steady-state for 50 mg/day amisulpride is reached between 3 and 4 days after starting administration. The PET examinations were performed 4 h after the morning dose, well before the plasma half-life of amisulpride which is 17 h (Dufour and Desanti 1989). Thus, at the second scan, treated patients had been receiving amisulpride daily for at least 2 weeks, and were in a pharmacokinetic steady-state condition.

Other authors have reported a theoretical curvilinear relationship between the amount of neuroleptic in the plasma and the D_2 receptor occupancy, with a curve plateauing above 85% occupancy; above this level, a marked increase of the dose regimen should not greatly modify the D_2 receptor blockade. However, when the D_2 occupancy is lower (e.g. less than 30%), small changes in neuroleptic dosage should be sufficient to provoke considerable variations of the D_2 receptor occupancy (Farde et al. 1988). The data obtained here in patients treated with various doses of amisulpride uphold this type of dose-occupancy relationship.

Low doses of amisulpride (50–100 mg a day) prescribed for treatment of negative symptoms, induced an average occupancy of striatal D_2 receptors of 14±9% (range: 4–26%). This low degree of D_2 occupancy, observed in a sample of the patients included in a therapeutic trial of amisulpride on negative schizophrenic symptoms, does not mean that the activating effect is mediated exclusively by the striatal D_2 receptors. Indeed, since amisulpride has a high affinity only for both D_2 and D_3 receptors (Scatton et al. 1994), the activating effect could be mediated by the D_3 receptor, or by interaction with these two types of receptors in extrastriatal structures. Interestingly, the ^{14}C-amisulpride concentration was reported higher in extrastriatal structures than in striatum, in animals studied ex vivo (Dufour and Desanti 1989); in addition, amisulpride displays a certain degree of limbic selectivity since it is 3-fold more potent in inhibiting the binding of ^{3}H-raclopride to D_2 receptors in the limbic system than in the striatum of the rat (Scatton et al. 1995).

Our data indicate that amisulpride doses of 630–910 mg/day will result in D_2 receptor occupancy of 70–80% (Fig. 1), a level of occupancy suggested as an optimal interval for treatment of psychotic symptoms (Farde et al. 1995). Our data further indicate that amisulpride doses of 1107 mg/day will lead to D_2 receptor occupancy of 85%, a level of occupancy which has been associated with elevated extrapyramidal side-effects (Farde et al. 1992). It should be noted, however, that chronic neuroleptization by classical neuroleptics in animal models causes an up-regulation of D_2 dopamine receptors (Burt et al. 1977) which could theoretically lead to an underestimation of the striatal D_2 receptor occupancy. Such up-regulation is probably dose-dependent, and is more likely to occur in patients treated with high doses. At high occupancy levels (e.g. 80%) this underestimation would be a few percent, and has been reported to be 7% with sulpiride (Farde et al. 1992). Hence, if underestimation of 7% in occupancy is present for the highest occupancy level, a new fit of the dose-occupancy curve predicts that the optimum D_2 receptor occupancy would be reached with oral amisulpride doses ranging between 559 and 752 mg amisulpride a day. Also, the occupancy associated with greater risk of extrapyramidal side-effects would be 878 mg/day. However, such an upregulation has not been observed in limbic regions in animals treated with high doses of amisulpride (Scatton et al. 1994).

In conclusion, our data suggest that effective doses for treating positive symptoms with amisulpride can be not only significantly lower than the upper limit of the standard dosage range (standard range: 600–1200 mg/day), but also lower than levels at which extrapyramidal side-effects may begin. This study illustrates the capacity of in vivo receptor imaging to provide patient-specific data on neuroleptic dose range finding.

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