abnormalities, or both, may be considered candidates for either hemispherectomy or callosotomy. Both interventions have proved to be successful strategies (*21*). Ictal rCBF SPECT, in particular, showed focal to lobal hyperperfusion in all our patients. On the basis of the small number of patients, this finding cannot be considered a recommendation for lobectomy as an alternative approach; however, larger study populations might show the ability of ictal SPECT to identify some patients who might also benefit from more restrictive surgery.

CONCLUSION

Technetium-99m-ECD is a valuable tool for the investigation of childhood epilepsy, and application of the tracer appears to be safe. Generally, both interictal and ictal rCBF SPECT should be performed whenever possible. In childhood epilepsy, there are two major indications for the application of rCBF SPECT if the intent is to identify only the epileptogenic area: (a) the acceleration of ECoG application in patients with normal MRI scan results or low seizure frequency, or both, to shorten the hospital period of the child; and (b) to avoid ECoG in patients with focal MRI abnormalities that match ictal hyperperfusion seen on rCBF SPECT. Furthermore, interictal ^{99m}Tc-ECD SPECT might prove helpful in estimating postsurgical clinical outcome (e.g., seizure frequency or memory impairment) (*12*).

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Iodine-123-Iodobenzamide Binding in Parkinsonism: Reduction by Dopamine Agonists but Not L-Dopa

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The aim of the present study was to investigate the effect of treatment with L-Dopa or a dopamine agonist, or both, on specific striatal ^{123}I-iodobenzamide (IBZM) binding using an intraindividual longitudinal design. **Method:** We prospectively studied the effect of dopaminomimetic treatment on specific [^{123}I]IBZM binding measured by SPECT in 29 patients with a clinical diagnosis of Parkinson's disease, none of whom had previously received dopaminomimetic drugs. The patients had been selected on the basis of normal subsequent specific [^{123}I]IBZM binding, semiquantitatively calculated as the basal ganglia/frontal cortex ratio, and a positive response to the dopamine agonist apomorphine before initiation of dopaminomimetic therapy. A second ^{123}I-IBZM SPECT investigation was performed after 3–6 mo of treatment with L-Dopa or a dopamine agonist, or both. **Results:** Specific [^{123}I]IBZM binding was unchanged in 10 patients treated with L-Dopa alone. However, after treatment with a dopamine agonist there was a significant decline in specific [^{123}I]IBZM binding ($p < 0.05$). After treatment with a combination of L-Dopa and a dopamine agonist, specific [^{123}I]IBZM binding was reduced without reaching a level of significance ($p = 0.08$). **Conclusion:** Short-term treatment with a dopamine agonist but not with L-Dopa reduces specific [^{123}I]IBZM binding. Therefore, before performing an [^{123}I]IBZM SPECT scan in patients previously treated with dopaminomimetic drugs, dopamine agonists should be discontinued.

Key Words: Parkinson's disease; diagnosis; iodine-123-iodobenzamide; SPECT; L-Dopa; dopamine agonist

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Iodine-123-iodobenzamine (IBZM) SPECT is a predictor of dopaminergic responsiveness in previously untreated patients with parkinsonism (*1*). This capacity may also help to differ-

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entiate patients with Parkinson's disease (PD) from those with related basal ganglia disorders, such as multiple-system atrophy (MSA) with predominant parkinsonism (MSA of the striatonigral type) (*2,3*) or progressive supranuclear palsy (PSP) (*4*). In the latter patients, in contrast to those with PD, the striatum is affected, and response to dopaminomimetic drugs is usually poor (*5*).

There are conflicting reports concerning the effect of dopaminomimetic drugs on dopamine-D2 receptor binding in vivo as measured by PET or SPECT (*6–9*).

Therefore, we prospectively investigated the effect of L-Dopa or a dopamine agonist, or both, on specific [^{123}I]IBZM binding after 3–6 mo of treatment in previously untreated patients with clinically diagnosed PD.

MATERIALS AND METHODS

Patients

Twenty-nine previously untreated patients (Hoehn and Yahr stages I to III) were investigated. All patients presented with clinical signs compatible with Parkinson's disease according to the United Kingdom (Parkinson's Disease Society) brain bank criteria (*10*). These patients had normal [^{123}I]IBZM binding and a positive response to apomorphine before the initiation of oral therapy with L-Dopa, lisuride, bromocriptine or pramipexole. Lisuride, bromocriptine and pramipexole are all dopamine agonists that act mainly by stimulation of the dopamine-D2 receptor. Ten patients (mean age 64.2 yr, range 40–75 yr) received L-Dopa (300–600 mg daily, plus PDI) alone; 11 patients (mean age 56.7 yr, range 44–73 yr) received lisuride (0.8–1.6 mg daily, 10 patients) or pramipexole alone (1 mg daily, 1 patient); and 8 patients (mean age 55.8 yr, range 42–70 yr) received a combination of L-Dopa (200–450 mg daily) and a dopamine agonist (lisuride, 0.6–1.2 mg daily, 6 patients, or bromocriptine, 7.5 mg daily, 2 patients). There was no significant difference in age between the three patient groups (analysis of variance, p = ns). All patients improved clinically under these treatments. A second [^{123}I]IBZM SPECT investigation was performed after 3–6 mo of treatment. Patients continued taking their daily dose even on the day of the second study. All patients have been followed up for at least 2 yr.

All patients underwent MRI scanning, which did not show any frontal atrophy or marked vascular lesions. A few white matter lesions were present in 17 patients.

SPECT Imaging

All patients gave informed consent before the [^{123}I]IBZM SPECT study.

Iodine-123-IBZM binding was assessed by 2 hr after intravenous injection of 185 MBq [^{123}I]IBZM (3-iodo-6-methoxybenzamide). The specific activity of [^{123}I]IBZM was 195–222 TBq/mmole. A rotating dual-head gamma camera with a high-resolution collimator and a commercially available computer system were used for acquisition and data processing. The head was positioned in a special headholder and fixed with strips. Data were collected for 60 projections (360° rotation) in a 64 × 64 matrix. The acquisition time was 50 sec per projection. Image reconstruction was performed by filtered backprojection (Butterworth filter). Selected transverse slices (slice thickness 6.0 mm) were corrected for attenuation as described elsewhere (*11*). For semiquantitative evaluation of specific tracer uptake, regions of interest (ROIs) were placed over the basal ganglia (isocontour ROIs with a threshold of 80% of the striatal maximum) and the frontal cortex (irregular ROIs). A basal ganglia-to-frontal cortex activity ratio was calculated. The size of all ROIs was at least twice full width at half maximum (14 mm). There was no significant change in ROI size between the scans before and during treatment (number of pixels before treatment: 40 ± 12; during treatment 38 ± 11 [mean ± s.d.]; p = ns. by Wicoxon Signed Rank). A computer program for superimposing MRI and SPECT images was not available; such a program would have enabled more accurate determination of the ROIs. We did not observe any adverse reactions to intravenous injections of [^{123}I]IBZM.

Normal specific [^{123}I]IBZM binding was assessed in 14 control subjects and measured as 1.54 ± 0.05.

The diagnosis of PD is supported by a clear improvement in clinical signs under dopaminomimetic therapy. The response to apomorphine, a potent dopamine agonist, predicts this benefit from oral dopaminomimetic therapy (*12,13*).

Testing with the dopamine agonist apomorphine was performed after [^{123}I]IBZM SPECT, as previously described (*12–14*). Patients were rated clinically using part III of the Unified Parkinson's Disease Rating Scale (UPDRS) before and 30 min after subcutaneous injection of 2–5 mg apomorphine. Apomorphine test results were considered positive in the case of a reduction in UPDRS scores by at least 20% and negative for a reduction of less than 10%. If the reduction in UPDRS scores was between 10% and 20%, or if side effects precluded an adequate rating, the test results were considered equivocal. Testing with apomorphine was generally well tolerated. The investigator (JS) performing the apomorphine test had no knowledge of the [^{123}I]IBZM SPECT results. Likewise, the investigator (KT) calculating the basal ganglia/frontal cortex (BG/FC) ratios had no knowledge of the clinical data and the results of the apomorphine test. The Wilcoxon Signed Rank test was used for statistical analysis.

RESULTS

Twenty-nine patients (mean age 59.1 yr, range 40–75 yr) previously untreated with dopaminomimetic drugs were investigated before and after therapy with L-Dopa or a dopamine agonist, or both. Clinical rating performed after a mean follow-up period of 6 mo revealed a mean reduction in UPDRS scores by 20% in patients treated with L-Dopa, by 15% in patients treated with a dopamine agonist alone and by 40% in patients who received a combination of L-Dopa and a dopamine agonist.

Treatment with L-Dopa alone did not reduce specific [^{123}I]IBZM binding (pretreatment BG/FC ratio: 1.50 ± 0.06 [mean ± s.d.]; post-treatment BG/FC ratio: 1.49 ± 0.07; n = 10; p = ns (Fig. 1). Treatment with a dopamine agonist alone

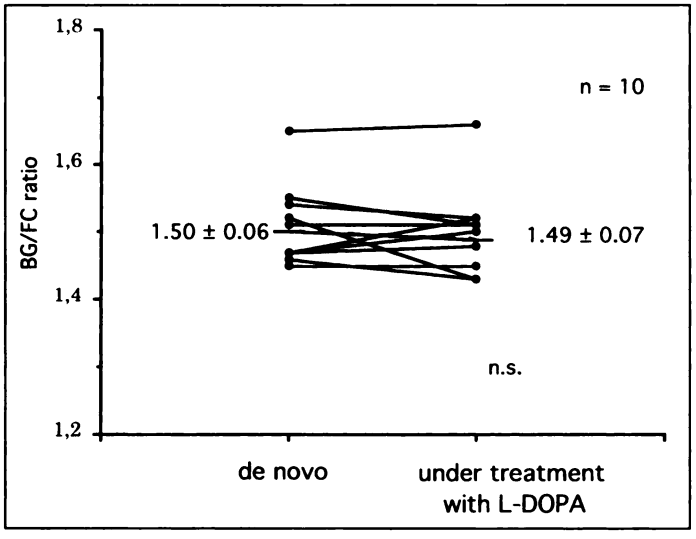

FIGURE 1. Iodine-123-IBZM SPECT results in previously untreated patients with PD (de novo) before (left) and after (right) treatment with L-Dopa for 3–6 mo. BG/FC = basal ganglia-to-frontal cortex ratio.

resulted in a significant reduction of specific [^{123}I]IBZM binding (pretreatment BG/FC ratio: 1.51 ± 0.03; post-treatment BG/FC ratio: 1.43 ± 0.08; n = 11; $p < 0.05$) (Fig. 2). Treatment with a combination of L-Dopa and a dopamine agonist led to reduction of specific [^{123}I]IBZM binding, which, however, failed to reach statistical significance (pretreatment BG/FC: 1.57 ± 0.09; post-treatment BG/FC: 1.51 ± 0.08; n = 8; p = 0.08 [ns]) (Fig. 3). When all patients treated with a dopamine agonist (alone or in combination with L-Dopa) were considered, a highly significant reduction of specific [^{123}I]IBZM binding was detected (pretreatment BG/FC: 1.53 ± 0.07; post-treatment BG/FC: 1.47 ± 0.09; n = 19; $p < 0.01$). In contrast, there was no significant reduction of specific [^{123}I]IBZM binding when those patients treated with L-Dopa alone were combined with those patients who received L-Dopa and a dopamine agonist (pretreatment BG/FC: 1.53 ± 0.08; post-treatment BG/FC: 1.50 ± 0.07; n = 18; p = 0.07 [ns]). When all 29 patients were considered, we observed a significant decrease in specific [^{123}I]IBZM binding (pretreatment BG/FC: 1.52 ± 0.07; post-treatment BG/FC: 1.47 ± 0.08; $p < 0.05$). We did not observe a correlation of the daily dose of the dopamine agonist with the reduction of specific dopamine-D2 receptor binding, which may be explained by the relatively small number of patients.

Of all 29 previously untreated patients, none has developed clinical signs suggesting a disorder other than Parkinson's disease. After a mean clinical follow-up period of 3 yr (range 2–4 yr) since the beginning of dopaminomimetic therapy, all 29 patients still respond well to this treatment; however, 12 of these patients have since developed mild motor fluctuations.

DISCUSSION

The present report proposes that treatment for 3–6 mo with dopamine agonists but not with L-Dopa reduces specific [^{123}I]IBZM binding. Our results are in agreement with previous studies in patients with the clinical diagnosis of Parkinson's disease that reported a reduction of specific dopamine-D2 receptor binding under therapy compared with previously untreated patients (*6,8*). However, none of these previous studies tried to prospectively evaluate the effect of L-Dopa and dopamine agonists separately. The reduction of specific [^{123}I]IBZM binding is obviously due to treatment with dopamine agonists. The relatively short follow-up period allows us to conclude only that treatment with L-Dopa for this period of time does not change [^{123}I]IBZM binding. Long-term follow-up of these patients is needed to investigate whether treatment with L-Dopa for several years may reduce [^{123}I]IBZM binding. Two likely explanations for the reduction of [^{123}I]IBZM binding after treatment with dopamine agonists are: (a) displacement of the tracer from the receptor by competition or (b) downregulation of the receptor density. A similar study in previously untreated patients with Parkinson's disease using PET and the ligand ^{11}C-raclopride showed that the reduction of specific ^{11}C-raclopride binding after treatment with lisuride is reversed after 3 days of drug holiday (*9*). Thus, it is very likely that treatment with dopamine agonists, at least for 3–6 mo, causes displacement of the ligand from the receptor rather than receptor downregulation. To further investigate this question it may be necessary to perform Scatchard binding curves by measuring [^{123}I]IBZM binding at different doses of agonist. In the aforementioned PET study, the effect of oral treatment with a dopamine agonist did not lead to a reduction of specific dopamine-D2 receptor binding below normal levels (*9*). In our study, 6 of 11 patients showed a reduction of specific [^{123}I]IBZM binding below normal levels. This difference may be explained by the different binding capacities of the two tracers, inducing more pronounced displacement by dopamine agonists of [^{123}I]IBZM than ^{11}C-raclopride, and by the disadvantages of SPECT in terms of correcting for scatter and attenuation that lead to a less accurate quantification of receptor densities and a greater variability of intraindividual scans.

In all three treatment groups there were two patients who showed an increase in specific [^{123}I]IBZM binding after treatment. This increase may also point to the variability of intraindividual SPECT studies. An alternative explanation could be a further loss of dopaminergic drive, which may lead to less competition of endogenous dopamine with [^{123}I]IBZM at the receptor site in these patients. However, we were not able to find a correlation of clinical deterioration with this increased [^{123}I]IBZM binding. These limitations and the relatively small number of patients may also have precluded a dose-dependent effect of dopamine agonists on the reduction of specific [^{123}I]IBZM binding.

Previous SPECT studies in patients with L-Dopa or apomorphine-responsive parkinsonism have found normal as well as decreased specific [^{123}I]IBZM binding (*6,8*) and reported a

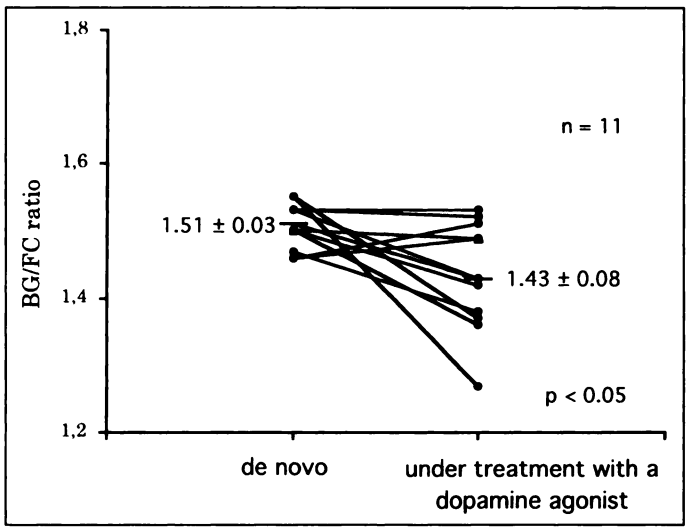

FIGURE 2. Iodine-123-IBZM SPECT results in previously untreated patients with PD (de novo) before (left) and after (right) treatment with a dopamine agonist for 3–6 mo. BG/FC = basal ganglia-to-frontal cortex ratio.

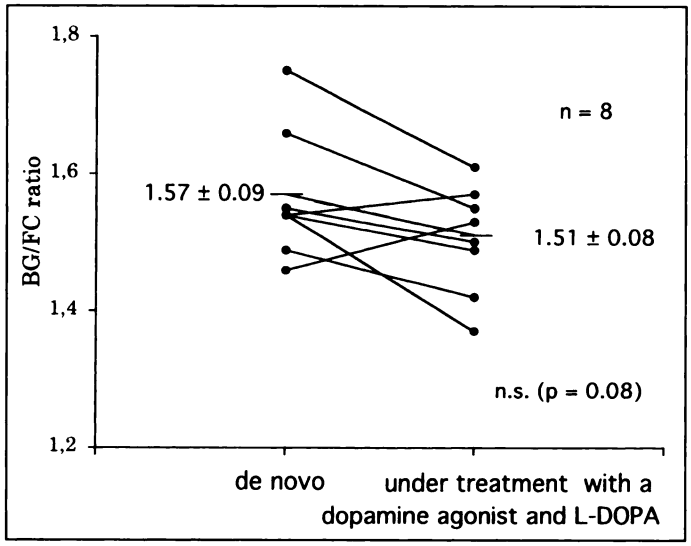

FIGURE 3. Iodine-123-IBZM SPECT results in previously untreated patients with PD (de novo) before (left) and after (right) treatment with L-Dopa and a dopamine agonist for 3–6 mo. BG/FC = basal ganglia-to-frontal cortex ratio.

marked overlap of binding results in untreated and treated patients with the clinical diagnosis of PD, MSA or PSP. However, in those studies the investigators did not distinguish untreated from treated patients with parkinsonism. On the basis of our data, we propose that therapy with dopamine agonists, by reducing [^{123}I]IBZM binding, may in part account for the reported overlap (*8*). In agreement with this hypothesis, a recent study that compared patients with the clinical diagnosis of probable MSA or PSP with normal age-matched volunteers showed little or no overlap of specific [^{123}I]IBZM binding (*4*).

CONCLUSION

Treatment with L-Dopa does not influence [^{123}I]IBZM binding, at least after a period of 3–6 mo, whereas dopamine agonists can reduce [^{123}I]IBZM binding. Because the reduction in specific ^{11}C-raclopride under treatment with a dopamine agonist reversed after a drug holiday of 3 days (*9*), we propose that these drugs be stopped about 7 days before an [^{123}I]IBZM SPECT investigation. Under this condition, [^{123}I]IBZM SPECT should equally predict dopaminergic responsiveness in patients previously treated with dopamimetic drugs compared with previously untreated patients. Reduction of specific [^{123}I]IBZM binding during treatment with a dopamine agonist most likely does not correlate with a functional striatal defect; rather, it reflects a pharmacological effect.

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Determination of Regional Rate Constants from Dynamic FDG-PET Studies in Parkinson's Disease

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Dynamic [^{18}F]fluorodeoxyglucose (FDG) PET was used in Parkinson's disease patients and normal controls to determine kinetic rate constants for FDG. The goal was to assess whether the metabolic decreases observed in Parkinson's disease are associated with transport or phosphorylation processes or both. **Methods:** Fluorine-18-FDG was administered to 18 Parkinson's disease and 15 normal control subjects. Dynamic PET scanning was performed for 1 h and rate constants were obtained by nonlinear, least-squares analysis. Regional glucose metabolic rate was calculated from the individually fitted rate constants and by two standard static scan analyses. **Results:** Global CMRglu was decreased in Parkinson's disease (mean reduction 22%), reaching statistical significance in all regions investigated. K_1 was significantly reduced in parietal cortex, temporal cortex and striatum while k_3 was significantly reduced only in parietal cortex. The rate constant k_2 was unchanged. **Conclusion:** K_1, k_3 and CMRglu all demonstrated greater deficits across the brain with progression of disease and development of dementia, particularly in the parietal and occipital cortex. This suggested that the metabolic disturbance may be a global dysfunction throughout the brain. Because altered rate constants are specifically taken into account, dynamic measurements has shown to provide higher sensitivity for detecting diminished glucose utilization in Parkinson's disease than static approaches.

Key Words: Parkinson's disease; dementia; kinetic rate constants; glucose metabolism

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In Parkinson's disease, little gross structural brain damage accompanies a specific biochemical lesion of the substantia nigra and its dopaminergic projections in the striatum (*1*). In living parkinsonian patients, PET has provided valuable pathophysiological information concerning altered pre- and postsynaptic compartments of the striatal dopaminergic neurotransmitter system (*2–4*). In early asymmetrical Parkinson's disease patients, [^{15}O]O_2 and [^{18}F]fluorodeoxyglucose (FDG) PET

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