[I-123]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease

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[123I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease

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Summary. We investigated the applicability [123I]FP-CIT SPECT for the assessment of the rate of dopaminergic degeneration in PD.

Twenty early-stage PD patients (age range 43–73 yr; mean age 55.4) were examined twice, a mean of 12 months apart. The mean annual change in the ratio of specific to nonspecific [123I]FP-CIT binding to the striatum was used as the outcome measure. The mean annual decrease in striatal [123I]FP-CIT binding ratios was found to be about 8% (of the baseline mean).

In order to demonstrate a significant effect ($p < 0.05$) of putative neuroprotective agent with 0.80 power and 50% of predicted protection within 2 years, 36 patients are required in each group, when the effects are measured by means of changes in [123I]FP-CIT binding ratios in whole striatum.

Our findings indicate that [123I]FP-CIT SPECT seems to be a useful tool to investigate the progression of dopaminergic degeneration in PD and may provide an objective method of measuring the effectiveness of neuroprotective therapies.

Keywords: Dopamine transporter imaging, Parkinson's disease, progression, [123I]FP-CIT SPECT.

Introduction

The pathophysiological hallmark of Parkinson's disease (PD) is a slow, progressive degeneration of dopaminergic neurons in the substantia nigra. Standard therapeutic interventions are aimed at replenishment of empty dopamine stores with levodopa or substitution with dopamine (DA) receptor agonists. However, in the long term this symptomatic therapy fails. Currently,

various neuroprotective agents are being developed, with the intention to slow down the degeneration of dopaminergic neurons. To evaluate the effectiveness of such neuroprotective agents, it is critical, however, to develop methods that can reliably measure progression of dopaminergic degeneration. PET and SPECT imaging might provide objective tools for measuring the effectiveness of putative neuroprotective agents and monitoring disease progression.

In several recent studies it has been shown, by using [^{18}F]dopa PET, that the presynaptic dopaminergic degeneration in PD is faster than in normal aging (Vingerhoets et al., 1994; Morrish et al., 1998). Iodine-123-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) SPECT has been used to investigate the presynaptic dopaminergic system in PD, by means of assessing the concentration of striatal DA transporters. Our previous studies have shown decreased striatal [^{123}I]FP-CIT binding in PD patients compared to healthy controls (Booij et al., 1997; Tissingh et al., 1998). At this moment, [^{123}I]FP-CIT SPECT is considered a highly reproducible technique (Booij et al., 1998), which might be of value in monitoring the progression of dopaminergic degeneration in PD. Therefore, we performed two [^{123}I]FP-CIT SPECT imaging series, 12 months apart, in a group of 20 early-stage, drug-naive PD patients, with the following purposes: 1) to investigate whether serial [^{123}I]FP-CIT SPECT imaging can be used as a marker of PD progression; 2) to give an indication of the sample size and imaging interval necessary to predict the effectiveness of a putative neuroprotective agent.

Materials and methods

Subjects

Twenty PD patients (16 males, 4 females), ranging in age at the time of the first image from 43–73 yr (mean age 55.4 yr) were examined by clinical assessment and [^{123}I]FP-CIT SPECT imaging. The diagnosis of PD was established according to the UK Parkinson's disease Society Brain Bank Criteria (Hughes et al., 1992). At the time of first imaging Hoehn and Yahr Staging Scale (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987) were used to assess the stage and severity of the disease, respectively. Clinical and demographical description of the patients is given in Table 1. Each patient was imaged on two occasions, with a mean scan-to-scan interval of 12 months and 3 weeks. Imaging was always performed on the same equipment and following the same protocol. All patients were drug-naive at the time of the first image, after which in 15 patients dopaminergic treatment (levodopa or DA receptor agonist) was initiated; 5 PD patients were still drug-naive at the time of the second SPECT image. The patients gave written informed consent for the study, which was approved by the medical ethics committee of the hospital.

SPECT camera

The Strichman Medical Equipment 810X system was used for SPECT imaging. The system is equipped with 12 individual crystals, each with a focussing collimator. The transaxial resolution of this camera is 7.6 mm full width at half maximum of a line source in air (Booij et al., 1997). The energy window was set at 135–190 keV. Data acquisition took place in a 128 × 128 matrix.

Table 1. Clinical and demographical data of 20 PD patients during first imaging session

	Mean	SD	Min	Max
Age (years)	55.4	9.9	43	73
PD duration (years)	2.5	1.3	0.5	5
Hoehn and Yahr stage	1.6	0.6	1	2.5
UPDRS motor score	16.5	6.9	8	35

PD Parkinson's disease; *UPDRS* Unified Parkinson's Disease Rating Scale; *SD* standard deviation; *Min* minimum; *Max* maximum

SPECT imaging

All patients received potassium iodide orally in order to block thyroid uptake of free radioactive iodide (three doses of 40 mg on the day before imaging and 80 mg just before imaging). [123I]FP-CIT (specific activity >185 MBq/nmol; radiochemical purity >99%) was injected intravenously at an approximate dose of 110 MBq. 123I labeling of FP-CIT was performed by Amersham Cygne (Technical University Eindhoven, The Nether-lands), using the trimethylstannyl precursor of FP-CIT obtained from Research Biochemicals International (Natick, MA). Image acquisition was always started at 3 hr after injection of the radioligand (Booij et al., 1999). Slices were acquired during 300 s periods, after positioning of the patient's head in the camera, with beams from gantry-mounted lasers oriented parallel to the canthomeatal line (CM line), from the CM line to the vertex using a interslice distance of 10 mm. During the second image session, all efforts were made to position the patient's head in the camera conform to the position during the first image session. In order to do that, the distances from the meatuses of the ears and from the orbital angles to the position of the laser beams were recorded. In previous studies we showed that this procedure is highly reproducible (Booij et al., 1998). A linear attenuation correction, based on absorption length of 95 mm was applied. The images were automatically reconstructed with a variable filter, according to the level of counts per slice (Booij et al., 1997). The measured concentration of radioac-tivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml).

Data processing

For analysis of striatal [123I]FP-CIT binding, two transversal slices representing the most intense striatal binding were summed. A standard region of interest (ROI) template, constructed manually according to a stereotactic atlas including fixed regions for whole striatum and occipital cortex, was placed bilaterally on the combined image (Matsui and Hirano, 1978). Small variations of individual brains required movement of the fixed regions of interest, without changing size and shape, within the template for optimal fitting. Estimates of specific striatal binding were made by subtracting occipital counts (non-specific binding) from striatal counts. The ratio of specific to non-specific striatal [123I]FP-CIT binding was then calculated (Laruelle et al., 1994).

Statistics

Relationships between variables were measured using Spearman rank correlation. Wilcoxon Signed Ranks Test was used to examine the change between baseline and follow-up imaging results and to compare the change in [123I]FP-CIT binding ratio in medicated and non-medicated patients. The mean annual rate of decline in [123I]FP-CIT binding ratios was expressed as a percentage of the baseline image and was calculated for each patient using the following formula:

$$\frac{\left(\text{SPECT image 2} - \text{SPECT image 1}\right)}{\text{SPECT image 1}} \times 100\%$$

Power analysis was performed in order to estimate the sample size and the image interval required to demonstrate a significant neuroprotective effect of agents with various degrees of predicted protection. The analysis was performed assuming the annual rate of dopaminergic degeneration based on the data obtained in the present study. Standard deviation of the mean annual change in [123I]FP-CIT binding was used as a measure of variance. The determination of sample size was performed according to the normogram of Altman (1991).

In case of multiple comparisons the Bonferroni correction was used. Each p-value marked with "*" indicates significance after Bonferroni correction. Significance was assessed at $p < 0.05$ level.

Results

The binding ratios during the first series of images was 59% for the ipsilateral striatum and 46% for the contralateral striatum, when compared to control data obtained in our previous study (Tissingh et al., 1998). Hoehn and Yahr stage of the patients at the time of the first image was significantly correlated with baseline [123I]FP-CIT binding ratios in the regions of interest (Spearman rank correlation; correlation coefficients were -0.66 ($p < 0.002$) and -0.62 ($p < 0.003$) for the ipsilateral and contralateral striatum, respectively.

A decrease in [123I]FP-CIT binding ratios between the two images was found in the regions of interest (Table 2). There was a significant decrease in [123I]FP-CIT binding ratios in the whole striatum (from 1.27 ± 0.32 to 1.15 ± 0.28; Fig. 1), ipsilateral striatum (from 1.45 ± 0.37 to 1.31 ± 0.29) and contralateral striatum (from 1.09 ± 0.29 to 0.99 ± 0.28; Table 2). The relative annual rate of decrease in [123I]FP-CIT binding ratios was about 8% of the baseline value in striatal regions.

No correlation was found between the rate of progression in the regions of interest and the duration of the PD symptoms, nor the severity of the disease expressed by means of UPDRS motor score.

No statistically significant difference was found in the annual rate of decrease in [123I]FP-CIT binding ratios between medicated and non-medicated PD patients.

Table 2. The mean annual change in the ratio of specific to nonspecific [123I]FP-CIT binding

	Mean image 1	Mean image 2	Mean relative change (%)
Striatum whole	1.27 ± 0.32	1.15 ± 0.28	-8.08 ± 12.22*
Striatum ipsi	1.45 ± 0.37	1.31 ± 0.29	-8.09 ± 13.92*
Striatum contra	1.09 ± 0.29	0.99 ± 0.28	-8.35 ± 12.71*

ipsi ipsilateral; *contra* contralateral (side opposite that of initial presentation of motor signs). *Significant relative difference between the mean values of two imaging assessments (Wilcoxon Signed Ranks Test; $p < 0.05$, after Bonferroni correction)
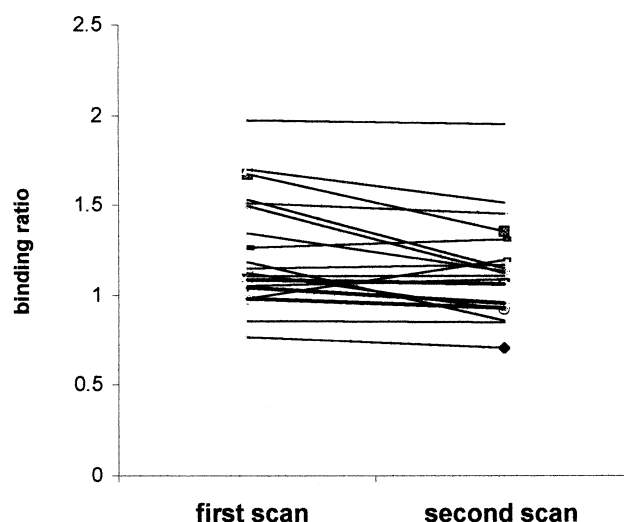
Fig. 1. Individual ratio's of specific to non-specific [123I]FP-CIT binding for the whole striatum (mean ipsilateral and contralateral sides) obtained in 20 early PD patients at baseline (first scan) and one year later (second scan)

Power analysis indicated that in order to detect a significant effect of a neuroprotective agent with 0.80 power and 50% of predicted protection within 1 year, 143 patients would be required in each group, when the effects are measured by means of changes in [123I]FP-CIT binding ratios in the whole striatum. For a trial with an agent with 30% of predicted neuroprotection 396 patients in each group would be required. Assuming linear decline of dopaminergic function, it was calculated that extension of the scanning interval to 5 years reduces the required sample size to 6 patients in each group, for a trial with an agent with 50% of predicted protection, and 16 patients in each group, for a trial with 30% of predicted protection (Table 3).

Table 3. Indication of the sample size and scan-to-scan interval required to give 80% power of detecting a significant ($p < 0.05$) effect of a neuroprotective agent, with predicted protection of 50% and 30% (assuming the reported relative rate of dopaminergic degeneration, in each region separately)

ROI	Time interval					
	1 year protection		2 years protection		5 years protection	
	50%	30%	50%	30%	50%	30%
Striatum whole	143	396	36	99	6	16
Ipsi	185	514	47	129	8	21
Contra	144	399	37	100	6	16

ROI region of interest; *ipsi* ipsilateral; *contra* contralateral (side opposite that of initial presentation of motor signs)

Discussion

This is the first study investigating the utility of [123I]FP-CIT SPECT for serial evaluations in a group of early-stage PD patients.

The baseline [123I]FP-CIT binding ratios in ipsilateral and contralateral striatum were in PD patients significantly lower than in control subjects (Tissingh et al., 1998). Moreover, a significant correlation was found between baseline [123I]FP-CIT binding ratios and the disease severity expressed as Hoehn and Yahr stadium. These results are in line with the findings of a previous study (Booij et al., 1997), indicating that the [123I]FP-CIT SPECT is a sensitive marker of disease severity in PD. Also the test/retest reproducibility of [123I]FP-CIT SPECT has recently been investigated by Booij et al. (1998) who demonstrated that [123I]FP-CIT SPECT imaging is a highly reproducible measure of striatal DA transporters in PD patients and indicated the suitability of this method in the serial evaluation of dopaminergic degeneration in PD.

In the present study, we showed that the mean annual rate of dopaminergic degeneration in striatum reached statistical significance and was about 8% of the baseline mean. Recently, several SPECT studies appeared on measuring the disease progression in PD using different dopamine transporter radiotracers, one of them being [123I]β-CIT. Overall, these studies have successfully demonstrated the applicability of dopamine transporter imaging to assess disease progression in PD (Marek et al., 1997; Pirker et al., 1998; Winogrodzka et al., 1999; Staffen et al., 2000). Interestingly, also a PET study, using [18F]CFT as a radiotracer for the dopamine transporter, showed that the rate of annual decline in early PD patients, was 13,1% and 12,5% in the putamen and caudate nucleus, respectively (Nurmi et al., 2000). In addition, several [18F]DOPA PET studies showed progression of disease in PD (Vingerhoets et al., 1994; Morrish et al., 1996, 1998). As already discussed by Morrish et al. (1996, 1998), the rate of decline in [18F]DOPA uptake varied (from 0.4 to 4.7%) depending on the outcome measure and analysis method. Although our present data suggest a faster rate of decline compared to the striatal [18F]DOPA studies, one has to keep in mind that one can not directly compare striatal dopamine transporters densities and striatal [18F]DOPA uptake values. However, it would of interest to perform a study comparing the rate of progression in PD patients by injecting each subject both by a dopamine transporter radiotracer as well as with [18F]DOPA.

Van Dyck et al. (1995) investigated age-related changes in DA transporter binding with the cocaine analogue [123I]β-CIT SPECT in human controls and found approximately 8% decline per decade. [123I]β-CIT SPECT has been shown to detect loss of DA transporters comparably to [123I]FP-CIT SPECT (Booij et al., 1997). In this context, our results indicate that the rate of progression of dopaminergic degeneration is much faster in PD than in normal aging.

The present study allows sample size calculations for future studies on the evaluation of neuroprotective treatments (Table 3). We estimated that, in

order to find a significant effect of a neuroprotective agent with 80% power and 50% of predicted protection within 1 year, 143 patients are required in each group, when the effects are measured in the whole stiatum. For a trial with an agent with 30% of predicted protection 396 patients are required. As expected, extending the scanning interval to 5 years reduces the required sample size remarkably. All above mentioned smaple size calculations for future studies on the effect of neuroprotective treatments are based on the assumption of a linear rate of dopaminergic degeneration through the initial course of the disease. The results of our study are based on two assessments (one year apart) of striatal [123I]FP-CIT binding in a group of twenty early PD patients. The linear evolution seems a reasonable approximation for the relatively brief period of time involved in the present study. However, more longitudinal assessments are needed in order to determine properly the pattern of disease progression in PD. Several studies (Staffen et al., 2000; Morrish et al., 1996) suggested that the pattern of disease progression in PD might be exponential instead of linear. This suggestion is of importance since it may influence the results of our calculations on sample size for future studies on the effect of neuroprotective treatments. If the degeneration shows an exponential course, slowing down in the later disease stadium (Staffen et al., 2000), then a larger sample size may be required in order to detect the same neuroprotective effect.

The possible medication effects should be discussed as 15 patients in the present study were under dopaminergic medication (levodopa or DA receptor agonists) at the time of the second image. However, Laruelle et al. (1993) showed that infusion of high doses levodopa failed to displace striatal [123I]β-CIT binding in non-human primates. In line with this observation, Innis et al. (1999) demonstrated recently that treatment with levodopa or L-selegiline in PD patients causes neither significant occupancy nor modulation in the number of striatal DA transporters labeled with [123I]β-CIT. Likewise, D_2 receptor agonists were indicated not to have any influence on binding of radioligands to the dopamine transporter (Dresel et al., 1988; Vander Borght et al., 1995; Little et al., 1996; Ahlskog et al., 1999). Moreover, we recently observed no significant influence of D_2 receptor agonists on striatal [123I]β-CIT binding in PD patients (A. Winogrodzka, unpublished observations). Finally, in the present study the rate of decrease in [123I]FP-CIT binding after 1 year was comparable between medicated and non-medicated PD patients, which also may indicate no significant effects of dopaminergic medication. Therefore, measurement of dopaminergic degeneration in the present study was based on the assumption that dopaminergic treatment has no significant influence on [123I]FP-CIT binding to striatal DA transporters.

In conclusion, our study demonstrates for the first time that [123I]FP-CIT SPECT allows to measure the rate of dopaminergic degeneration in early-stage PD patients. Our observations, in combination with the fact of wide availability of the SPECT technique, makes [123I]FP-CIT SPECT a good alternative for [18F]DOPA PET as a method for estimating the effectiveness of putative neuroprotective therapies in large clinical trials.

Acknowledgement

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