

[¹²³I]β-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease

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Objectives: To examine the validity of [¹²³I]β-CIT SPECT for monitoring the progression of dopaminergic degeneration in Parkinson's disease; to investigate the influence of short term treatment with D₂ receptor agonists on striatal [¹²³I]β-CIT binding; and to determine the sample size and frequency of SPECT imaging required to demonstrate a significant effect of a putative neuroprotective agent.

Methods: A group of 50 early stage Parkinson's disease patients was examined. Two SPECT imaging series were obtained, 12 months apart. The mean annual change in the ratio of specific to non-specific [¹²³I]β-CIT binding to the striatum, putamen, and caudate nucleus was used as the outcome measure.

Results: A decrease in [¹²³I]β-CIT binding ratios between the two images was found in all regions of interest. The average decrease in [¹²³I]β-CIT binding ratios was about 8% in the whole striatum, 8% in the putamen region, and 4% in the caudate region. Comparison of scans done in nine patients under two different conditions—in the off state and while on drug treatment—showed no significant alterations in the expression of striatal dopamine transporters as measured using [¹²³I]β-CIT SPECT. Power analysis indicated that to detect a significant (*p* < 0.05) effect of a neuroprotective agent with 0.80 power and 30% of predicted protection within two years, 216 patients are required in each group when the effects are measured in the whole putamen.

Conclusions: [¹²³I]β-CIT SPECT seems to be a useful tool to investigate the progression of dopaminergic degeneration in Parkinson's disease and may provide an objective method of measuring the effectiveness of neuroprotective treatments. Short term treatment with a D₂ agonist does not have a significant influence on [¹²³I]β-CIT binding to dopamine transporters. If the latter finding is replicated in larger groups of patients, it supports the suitability of [¹²³I]β-CIT SPECT for examining the progression of neurodegeneration in patients being treated with D₂ receptor agonists.

The pathophysiological hallmark of Parkinson's disease is a slow, progressive degeneration of dopaminergic neurones in the substantia nigra.¹ Standard therapeutic interventions are aimed at replenishing empty dopamine stores with levodopa, or substitution with dopamine receptor agonists. However, in the long term this symptomatic treatment fails. Various neuroprotective agents are currently being developed with the intention of treating the cause of the disease and thereby delaying the degeneration of dopaminergic neurones. To evaluate the effectiveness of such agents, it is important to develop methods that can reliably measure progression of dopaminergic degeneration. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) could prove to be objective tools for measuring the effectiveness of putative neuroprotective agents and monitoring disease progression. For example, recent studies using [¹⁸F]dopa PET have shown that the presynaptic dopaminergic degeneration in Parkinson's disease is faster than in normal aging.^{2–4}

Since 1993, [¹²³I]β-CIT SPECT has been used to investigate the presynaptic dopaminergic system in Parkinson's disease by assessing the concentration of striatal dopamine transporters. Several studies have shown that decreased striatal [¹²³I]β-CIT binding correlates well with symptom severity.^{5,6} [¹²³I]β-CIT SPECT is now considered a highly reproducible technique which could be of value in monitoring the progression of dopaminergic degeneration in Parkinson's disease.^{7,8}

Our aim in this study was to investigate whether serial [¹²³I]β-CIT SPECT imaging can be used as a marker of Parkinson's disease progression. We undertook two [¹²³I]β-CIT SPECT imaging series 12 months apart in a group of 50 patients with early stage Parkinson's disease. We also estimated the sample

size and scan interval necessary to predict the effectiveness of a putative neuroprotective agent.

METHODS

Subjects

For the "progression study," a group of 50 patients with Parkinson's disease (31 men and 19 women) was examined by clinical assessment and [¹²³I]β-CIT SPECT imaging. The patients were recruited from the movement disorders unit of our outpatient clinic. The diagnosis of Parkinson's disease was established according to the UK Parkinson's Disease Society brain bank criteria.⁹ The mean (SD) age of the patients at the time of the first imaging was 56.7 (9.3) years, range 37 to 71. The mean duration of Parkinson's disease was 2.7 (2.2) years. The Hoehn and Yahr staging scale¹⁰ and the unified Parkinson's disease rating scale (UPDRS)¹¹ were used to assess the stage and severity of the disease at the time of first imaging. A detailed clinical and demographic description is given in table 1. Each patient was imaged on two occasions, with a mean scan to scan interval of 51 (7) weeks.

All patients gave written informed consent to the research protocol, which was approved by the medical ethics committee of the hospital.

Drug treatment

All patients in the "progression study" were drug-naïve at the time of the first scan, after which dopaminergic treatment (levodopa or a D₂ receptor agonist) was initiated.

A previous study in patients with Parkinson's disease showed no significant effects of subchronic administration of

Table 1 Clinical and demographic data on 50 patients with Parkinson's disease

| | |
|------------------------------|------------|
| Male/female | 31/19 |
| Age at first imaging (years) | 56.7 (9.3) |
| Age at onset (years) | 54.0 (9.8) |
| Duration of disease (years) | 2.7 (2.2) |
| Hoehn and Yahr stage | 1.9 (0.6) |
| UPDRS motor score | 19.2 (6.7) |

Data are n or mean (SD).
UPDRS, unified Parkinson's disease rating scale.

levodopa or L-selegiline on striatal [¹²³I]β-CIT binding to dopamine transporters.¹² Likewise, D₂ receptor agonists appear to have no influence on the expression of the striatal dopamine transporter.^{13–15} However, the effects of these drugs on striatal [¹²³I]β-CIT binding in Parkinson's disease have only been examined in one study.²⁸

Effect of D₂ receptor agonist on striatal [¹²³I]β-CIT binding

In order to assess the effects of D₂ receptor agonists on striatal [¹²³I]β-CIT binding in our study, nine patients with Parkinson's disease (seven male and two female; age 61.5 (8.2) years; duration of Parkinson's disease 3.2 (1.5) years) were imaged twice: first, when not previously exposed to D₂ receptor agonist treatment or when withdrawn from it, and second, while on treatment with a D₂ receptor agonist. The scan to scan interval was two to five weeks.

Six of the patients had not previously received D₂ receptor agonist treatment at the time of the first imaging. In these six patients (protocol A), treatment with a D₂ receptor agonist (pergolide or pramipexol) was started one day after the baseline imaging, following an increasing schedule up to 2.0 mg/day for pergolide and 2.25 mg/day for pramipexol (table 2). In these patients, the second imaging was done after four to five weeks while they were on treatment with the D₂ receptor agonist. In the last week before the second imaging, the daily dose of the D₂ receptor agonist was maintained stable.

The other three patients in the D₂ receptor agonist assessment study were first imaged while on a stable dose of pergolide, which had been given as monotherapy for about a year. After the initial imaging, the drug was withdrawn for two to three weeks and the second imaging was done (protocol B).

The effects of D₂ receptor agonist treatment on [¹²³I]β-CIT binding measures and the treatment details of the patients are summarised in table 2.

SPECT camera

The Strichman Medical Equipment 810X system (Strichman Inc, Medfield, Massachusetts, USA) was used for SPECT

imaging. The transaxial resolution of this camera is 7.6 mm full width at half maximum of a line source in air.¹⁶ The energy window was set at 135–190 keV. Data acquisition took place in a 128 × 128 matrix.

SPECT imaging

The patients were given potassium iodide orally to block the thyroid uptake of free radioactive iodide. [¹²³I]β-CIT (specific activity > 185 MBq/nmol; radiochemical purity > 99%) was injected intravenously at an approximate dose of 110 MBq.¹²³I labelling, acquisition, attenuation correction, and reconstruction of images was done as described before.⁶ The measured concentration of radioactivity was expressed as Strichman medical units (SMUs; 1 SMU = 100 Bq/ml).

Image acquisition was always started 24 hours after the injection of the radioligand. Slices were acquired during 300 s periods after positioning the patient's head in the camera, with beams from gantry mounted lasers oriented parallel to the canthomeatal (CM) line, from the CM line to the vertex using an interslice distance of 10 mm. Imaging was always done using the same equipment and following the same protocol.

During the second image session, all efforts were made to ensure that the patient's head in the camera conformed to the position used during the first image session. To achieve this, 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.¹⁷

Data processing

For analysis of striatal [¹²³I]β-CIT binding, two transverse slices representing the most intense striatal binding were summed. A standard region of interest (ROI) template, constructed according to a stereotactic atlas and including fixed regions for caudate nucleus, putamen, whole striatum, and occipital cortex, was placed bilaterally on the combined image, as described previously.¹⁶ Estimates of specific striatal binding were made by subtracting occipital counts (non-specific binding) from total striatal counts. The ratio of specific to non-specific striatal [¹²³I]β-CIT binding was then calculated by dividing the specific striatal uptake by the occipital uptake. These binding ratios were also used to calculate comparable ratios for caudate nucleus and putamen.¹⁸

Statistics

The relation between the initial [¹²³I]β-CIT binding ratios and UPDRS was measured using the Spearman rank correlation. A paired samples two tailed *t* test was used to examine the change between baseline and follow up imaging results. The mean annual rate of decline in [¹²³I]β-CIT binding ratios was

Table 2 Effects of treatment with D₂ agonists on ratios of specific to non-specific [¹²³I]β-CIT binding in the whole striatum

| Patient No | Sex | Protocol | Drug (mg/day) | Striatal [¹²³ I]β-CIT binding ratio | |
|-------------------|-----|----------|-------------------|---|----------------------|
| | | | | On treatment | Drug-naive/withdrawn |
| 1 | F | B | Pergolide (1.0) | 1.72 | 1.79 |
| 2 | M | B | Pergolide (2.0) | 1.95 | 2.30 |
| 3 | M | B | Pergolide (2.0) | 1.63 | 1.66 |
| 4 | M | A | Pergolide (2.0) | 2.13 | 1.88 |
| 5 | F | A | Pramipexol (2.25) | 2.86 | 2.49 |
| 6 | M | A | Pergolide (1.5) | 1.86 | 2.10 |
| 7 | M | A | Pergolide (1.5) | 3.25 | 3.78 |
| 8 | M | A | Pergolide (2.0) | 2.22 | 2.22 |
| 9 | M | A | Pergolide (1.0) | 2.70 | 2.90 |
| Mean (SD): | | | | 2.26 (0.6) | 2.35 (0.70) |

F, female; M, male; protocol A, drug-naive at the time of first imaging; protocol B, approximately one year on monotherapy at the time of first imaging.

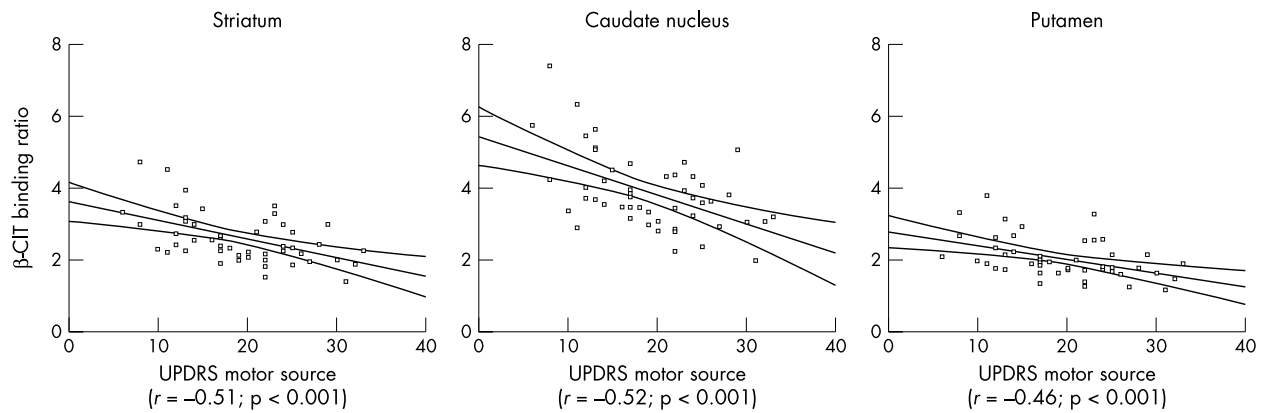


Figure 1 Correlation (Spearman rank) of the unified Parkinson's disease rating scale (UPDRS) motor score with specific to non-specific [^{123}I] β -CIT binding in striatum, putamen, and caudate nucleus in 50 patients with Parkinson's disease.

expressed as a percentage of the baseline [^{123}I] β -CIT binding ratios, and was calculated for each patient using the following formula:

$$\frac{[\text{follow up SPECT imaging minus baseline SPECT imaging}]}{[\text{baseline SPECT imaging}]} \times 100\%$$

For the assessment of the effects of D_2 receptor agonists on [^{123}I] β -CIT binding, the two conditions (on drug treatment, and either withdrawn from drug treatment or drug-naïve) were compared using the Wilcoxon signed ranks test.

Power analysis was undertaken to estimate the sample size and the scan interval required to demonstrate a significant neuroprotective effect of agents with various degrees of predicted protection. The analysis assumed an annual rate of dopaminergic degeneration based on the data obtained in the present study. The standard deviation of the mean annual change in [^{123}I] β -CIT binding was used as a measure of variance. Sample size was determined using Altman's nomogram.¹⁹

Significance was assumed at a probability (p) value of < 0.05 . In the case of multiple comparisons the Bonferroni correction was used.

RESULTS

No significant difference in age, disease severity, or [^{123}I] β -CIT binding measures was found between male and female subjects.

Progression of dopaminergic degeneration

The baseline ratios of specific to non-specific [^{123}I] β -CIT binding in all striatal regions of interest showed significant correlations with baseline motor UPDRS score (r_s values varying from -0.32 to -0.5 ; $p < 0.02$; fig 1). A decrease in [^{123}I] β -CIT binding ratios between the two consecutive scans was found in all regions of interest (table 3). There was a significant decrease in specific to non-specific [^{123}I] β -CIT binding ratios in the whole, ipsilateral, and contralateral striatum and putamen, this being most obvious in the whole putamen. The relative annual rate of decrease in [^{123}I] β -CIT binding ratios was about 8% in striatal regions, 8% in putaminal regions, and 4% in caudate regions.

No correlation was found between the rate of progression in all regions of interest and the baseline binding ratios, the duration of Parkinson's disease symptoms, or the severity of the disease expressed by the UPDRS motor score.

Effect of D_2 receptor agonist on striatal [^{123}I] β -CIT binding

Treatment with D_2 receptor agonists did not cause significant changes in the striatal [^{123}I] β -CIT binding ratios, as measured by serial SPECT imaging under the two different conditions

Table 3 Mean annual change in the ratio of specific to non-specific [^{123}I] β -CIT binding in 50 patients with early stage Parkinson's disease

| | Baseline ratio | Follow up ratio | Relative change |
|-------------------------|----------------|-----------------|-----------------|
| Striatum, whole | 2.6 (0.7) | 2.4 (0.7) | -7.6 (17.9)* |
| Putamen, whole | 2.1 (0.6) | 1.9 (0.5) | -8.4 (18.6)* |
| Caudate, whole | 3.9 (1.0) | 3.7 (1.1) | -4.5 (21.3) |
| Striatum, ipsilateral | 2.9 (0.8) | 2.6 (0.8) | -7.5 (17.6)* |
| Striatum, contralateral | 2.3 (0.6) | 2.1 (0.7) | -7.1 (20.7)* |
| Putamen, ipsilateral | 2.4 (0.7) | 2.2 (0.7) | -8.0 (17.9)* |
| Putamen, contralateral | 1.7 (0.5) | 1.6 (0.5) | -7.9 (25.2)* |
| Caudate, ipsilateral | 4.2 (1.1) | 4.0 (1.2) | -4.4 (21.2) |
| Caudate, contralateral | 3.6 (1.0) | 3.4 (1.1) | -4.5 (22.8) |

Values are mean (SD).

The relative change in [^{123}I] β -CIT binding ratios within one year was calculated using the formula: [follow up SPECT imaging minus baseline SPECT imaging]/[baseline SPECT imaging] \times 100%

*Significant relative difference between the mean values of two imaging assessments (paired samples two tailed t test; $p < 0.05$).

(protocol A and protocol B) described above: on treatment v drug naïve or withdrawn from drugs, 2.26 (0.6) v 2.35 (0.67); $p = 0.4$; table 2).

Power analysis

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 two years, 78 patients would be required in each group when the effects are measured by means of changes in [^{123}I] β -CIT binding ratios in the whole putamen. For a trial with an agent with 30% of predicted neuroprotection, 216 patients would be required. Assuming a linear decline in dopaminergic function, it was calculated that extending the scanning interval to five years reduces the required sample size to 13 patients in each group for a trial with an agent with 50% of predicted protection, and to 35 patients in each group for a trial with an agent with 30% of predicted protection (table 4).

DISCUSSION

This is one of the few [^{123}I] β -CIT SPECT studies done so far to investigate the value of the technique in monitoring the progression of Parkinson's disease by serial evaluation in a large group of patients with early stage disease.²⁰⁻²²

In agreement with other studies, we found significant correlations between [^{123}I] β -CIT binding ratios and UPDRS motor score in drug-naïve patients.⁵⁻⁶ The binding ratios obtained at the first series of imagings were approximately 35% of control for the putamen and 55% of control for the caudate nucleus.²³

Table 4 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)

| Region of interest | Time interval | | | | | |
|-------------------------|---------------------|------|----------------------|------|-----------------------|-----|
| | One year protection | | Two years protection | | Five years protection | |
| | 50% | 30% | 50% | 30% | 50% | 30% |
| Striatum, whole | 340 | 949 | 85 | 238 | 14 | 38 |
| Striatum, ipsilateral | 346 | 961 | 87 | 241 | 14 | 39 |
| Striatum, contralateral | 534 | 1483 | 134 | 371 | 22 | 60 |
| Putamen, whole | 310 | 863 | 78 | 216 | 13 | 35 |
| Putamen, ipsilateral | 312 | 866 | 79 | 217 | 13 | 35 |
| Putamen, contralateral | 636 | 1775 | 160 | 444 | 26 | 71 |
| Caudate, whole | 1395 | 3851 | 349 | 963 | 56 | 155 |
| Caudate, ipsilateral | 1485 | 4112 | 372 | 1028 | 60 | 165 |
| Caudate, contralateral | 1641 | 4545 | 411 | 1137 | 66 | 182 |

These results are in line with the findings of previous studies,⁵⁻⁶ indicating that the [¹²³I]β-CIT SPECT technique is a sensitive marker of disease severity in Parkinson's disease.

The test/retest reproducibility of [¹²³I]β-CIT SPECT has also recently been investigated by Seibyl *et al.*⁷ These investigators showed that [¹²³I]β-CIT SPECT imaging is a highly reproducible measure of striatal dopamine transporters in Parkinson's disease and suggested that the method would be suitable for the serial evaluation of dopaminergic degeneration.

In the present study, we showed that the mean annual rate of dopaminergic degeneration in striatum, and subregionally in the putamen, reached statistical significance at about 8%. These findings fit well with the results of recent PET and SPECT studies.^{4, 21, 24, 25} For example, Morrish *et al* and the Parkinson Study Group reported mean annual rates of dopaminergic degeneration in Parkinson's disease of 9% and 5%, respectively.^{4, 21} In addition, Van Dyck *et al* investigated age related changes in dopamine transporter binding with [¹²³I]β-CIT SPECT in human controls²⁶ and found approximately an 8% decline per decade. In this context, our results show that the rate of progression of dopaminergic degeneration is much faster in Parkinson's disease than in normal aging.

The mean rate of progression of the dopaminergic degeneration in the caudate was slower than in the putamen. This is in agreement with the results of cross sectional SPECT and PET studies, indicating that the function of the caudate nucleus in the early Parkinson's disease stages is relatively spared.

Though the patients in the present study were under dopaminergic drug treatment (levodopa or a D₂ agonist) at the time of the second imaging, Laruelle *et al* showed that infusion of high dose levodopa failed to displace striatal [¹²³I]β-CIT binding in non-human primates.²⁷ In line with this observation, Innis *et al* demonstrated recently that treatment with levodopa or L-selegiline in Parkinson's disease causes neither significant occupancy nor modulation in the number of striatal dopamine transporters labelled with [¹²³I]β-CIT.¹² Moreover, Ahlskog and coworkers²⁸ reported that short term treatment with the dopamine D₂ agonist pergolide did not significantly influence binding of [¹²³I]β-CIT to dopamine transporters in Parkinson's disease.

In order to assess the effects of D₂ agonists on [¹²³I]β-CIT binding to the dopamine transporters we also undertook sequential imaging in nine patients with Parkinson's disease under two different conditions: on D₂ agonist treatment, and drug-naïve or withdrawn from D₂ agonist treatment. Our results show that short term treatment with D₂ agonists did not cause any significant changes in the binding of [¹²³I]β-CIT to striatal dopamine transporters. This finding confirms the results of previous animal experiments investigating the

influence of several dopamine receptor agonists on the striatal dopamine transporter.¹³⁻¹⁵ Thus measurement of dopaminergic degeneration in the present study was based on the assumption that treatment with D₂ agonists or levodopa has no significant influence on [¹²³I]β-CIT binding to dopamine transporters. Nonetheless, all of these studies—including the present one—are limited by small sample sizes (and consequently by limited power), as well as by short duration, and therefore do not exclude the possibility that pharmacological effects could emerge in larger or longer term studies.

Several techniques are now available for imaging nigrostriatal dopaminergic neurones (for a review, see Booij and colleagues²⁹). In the present study, we used a radiotracer which binds to the dopamine transporter. This transporter is located exclusively on nerve terminals of dopaminergic cells. Several studies have shown that the loss of striatal dopamine transporters in Parkinson's disease is in concordance with the loss of nigrostriatal dopamine neurones.³⁰ In addition, necropsy studies of patients with Parkinson's disease have shown that measurements of dopamine transporter density are highly correlated with striatal dopamine levels.³¹ Experimental studies in rats and monkeys have also validated the fact that drug induced losses of nigrostriatal cells are correlated with loss of dopamine transporters, as measured by [¹²³I]/[¹²⁵I]β-CIT.^{32, 33} Moreover, several [¹²³I]β-CIT SPECT studies have shown loss of dopamine transporters in Parkinson's disease, and correlations between motor signs and severity of loss of these transporters.^{5, 6} These studies have shown the validity of using dopamine transporter imaging to assess the integrity of presynaptic dopaminergic nerve terminals in Parkinson's disease. In fact, β-CIT SPECT assesses the expression of dopamine transporters on surviving dopaminergic cells. Recently, an important study by Lee *et al* suggested that the dopamine transporter is downregulated on surviving dopaminergic neurones in Parkinson's disease.³⁴ This observation is in line with experimental studies suggesting that the loss of dopamine neurones is functionally compensated by an increase in synthesis and release of dopamine from surviving dopamine nerve terminals, as well as by a reduced rate of dopamine inactivation in presynaptic dopamine nerve terminals.³⁵ In the light of all these data, we cannot exclude the possibility in the present study that the loss of dopamine transporters in Parkinson's disease results from a combination of cell loss (and consequently loss of dopamine transporters) and downregulation of dopamine transporters on surviving neurones. However, if the loss of β-CIT binding to dopamine transporters in Parkinson's disease can be explained partly by downregulation, it seems unlikely that this regulation will disappear, whereas degeneration of dopaminergic neurones

will progress. Consequently, the possible occurrence of down-regulation on surviving dopaminergic nerve terminals in Parkinson's disease may not hamper the applicability of [¹²³I]β-CIT SPECT in monitoring disease progression.

Our study allows sample size calculations for future studies on the evaluation of neuroprotective treatments (table 4). The most extensive deterioration after one year was found in the whole putamen, indicating that in early Parkinson's disease, [¹²³I]β-CIT binding in this region is the most sensitive to changes in the rate of dopaminergic degeneration. We estimated that, in order to show a significant effect of a neuroprotective agent with 0.80 power and 50% of predicted protection within two years, 78 patients are required in each group when the effects are measured in the whole putamen. For a trial with an agent with 30% of predicted protection, 216 patients are required. As expected, extending the scanning interval to five years reduces the required sample size remarkably. All estimations are based on the assumption of a constant rate of dopaminergic degeneration through the initial course of the disease. The linear evolution seems a reasonable approximation for the relatively brief period of time involved in the present study. However, if the degeneration shows an exponential course, slowing down in the later disease stages (a reasonable hypothesis), then a larger sample size would be required to detect the same neuroprotective effect.

Conclusions

Our study shows that [¹²³I]β-CIT SPECT allows measurements of the rate of dopaminergic degeneration in early stage Parkinson's disease. Our observations, in combination with the wide availability of the SPECT technique, makes [¹²³I]β-CIT SPECT an alternative to PET as a method for estimating the effectiveness of putative neuroprotective treatments in large clinical trials. Our study also showed that short term treatment with D₂ agonists did not influence [¹²³I]β-CIT binding to dopamine transporters in a small group of patients. If replicated in larger groups of patients, this finding confirms the applicability of [¹²³I]β-CIT SPECT for examining the progression of dopaminergic degeneration in patients who are on these drugs.

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