Iodine-123-β-CIT and Iodine-123-FPCIT SPECT Measurement of Dopamine Transporters in Healthy Subjects and Parkinson's Patients

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Iodine-123-β-carbomethoxy-3 β-(4-iodophenyltropane) (CIT) has been used as a probe of dopamine transporters in Parkinson's disease patients using SPECT. This tracer has a protracted period of striatal uptake enabling imaging 14–24 hr postinjection for stable quantitative measures of dopamine transporters, and it binds with nanomolar affinity to the serotonin transporter. Iodine-123 fluoropropyl (FP)CIT is an analog of $[^{123}I]$-β-CIT and has been shown to achieve peak tracer uptake in the brain within hours postinjection and to provide greater selectivity for the dopamine transporter. The purpose of the present study was to compare $[^{123}I]$-β-CIT with $[^{123}I]$-FPCIT in a within-subject design. **Methods:** Six Parkinson's disease patients and five healthy control subjects participated in one $[^{123}I]$-β-CIT and one $[^{123}I]$-FPCIT SPECT scan separated by 7–21 days. Controls were imaged at 24 hr postinjection 222 MBq (6 mCi) $[^{123}I]$-β-CIT and serially from 1–6 hr postinjection 333 MBq (9 mCi) $[^{123}I]$-FPCIT. Two imaging outcome measures were evaluated: (a) the ratio of specific striatal activity to nondisplaceable uptake, designated V''_3, at each imaging time point; and (b) the rate of striatal washout of radiotracer expressed as a percent reduction per hr for $[^{123}I]$-FPCIT. In addition, venous plasma was obtained from the five control subjects after the $[^{123}I]$-FPCIT injection for analysis of radiometabolites. **Results:** Both $[^{123}I]$-FPCIT and $[^{123}I]$-β-CIT demonstrated decreased striatal uptake in Parkinson's disease patients compared with the controls with a mean of $V''_3 = 3.5$ and 6.7 for $[^{123}I]$-β-CIT (Parkinson's disease and controls, respectively) and a mean of $V''_3 = 1.34$ and 3.70 for $[^{123}I]$-FPCIT (Parkinson's disease and controls, respectively). For $[^{123}I]$-β-CIT, the mean Parkinson's disease values represented 52% of the control uptake, while the mean $[^{123}I]$-FPCIT value for Parkinson's disease patients was 37% of the control values. Analysis of $[^{123}I]$-FPCIT time-activity curves for specific striatal counts showed washout rates of 8.2%/hr for Parkinson's disease and 4.9%/hr for controls. **Conclusion:** These data suggest that SPECT imaging with $[^{123}I]$-FPCIT visually demonstrates reductions in striatal uptake similar to $[^{123}I]$-β-CIT. Iodine-123-FPCIT washed out from striatal tissue 15–20 times faster than $[^{123}I]$-β-CIT, and estimates of dopamine transporter loss in Parkinson's disease patients were higher for $[^{123}I]$-FPCIT than for $[^{123}I]$-β-CIT. This was most likely due to the faster rate of striatal washout and establishment of transient equilibrium binding conditions at the dopamine transporter, which the modeling theory suggests produces an overestimation of dopamine transporter density with relatively greater overestimates in healthy control subjects by $[^{123}I]$-FPCIT.

Key Words: dopamine; SPECT; iodine-123-β-carbomethoxy-3 β-(4-iodophenyltropane); dopamine transporter; Parkinson's disease; iodine-123-FP-carbomethoxy-3 β-(4-iodophenyltropane)

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Iodine-123-β-carbomethoxy-3 β-(4-iodophenyltropane) (CIT) binds with high affinity to dopamine ($IC_{50} = 1.6$ nM) and serotonin ($IC_{50} = 3.78$ nM) transporters, and it has been used as a SPECT probe in human and nonhuman primates (1–13). After intravenous administration of $[^{123}I]$-β-CIT in humans, decay-corrected striatal time-activity data showed a prolonged time to highest uptake occurring by 12–18 hr post-tracer injection and very slow rates of striatal washout of less than 0.5% per hr (5). Occipital and free parent plasma levels reached a plateau earlier than striatum and also demonstrated extremely slow rates of washout. The protracted stable level of parent activity in plasma and activity within brain compartments closely approximated equilibrium binding conditions at the dopamine transporter. Under such conditions, a simple ratio of specific striatal to background activity calculated during the plateau phase of uptake provided an outcome measure that was directly proportional to the dopamine transporter density (5).

Using this outcome measure, the healthy control subjects showed expected age-related reduction in uptake as a function of normal aging (6). Idiopathic Parkinson's disease patients demonstrated reduced $[^{123}I]$-β-CIT uptake compared with the age and gender-matched controls (2,7,8,10,11). In addition, patients with Hoehn-Yahr Stage I disease (hemiparkinsonism) had reductions of uptake in the striatum contralateral to symptom side and ipsilateral as well, suggesting the test is sensitive to changes in dopamine transporters before the appearance of clinical symptoms (11). In a series of 28 Parkinson's disease patients, $[^{123}I]$-β-CIT SPECT uptake was correlated with symptom severity as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) (7).

Nonetheless, $[^{123}I]$-β-CIT suffers from two potential drawbacks. First, the ligand binds with nanomolar affinity at the 5-hydroxytryptamine (HT) transporter, potentially confounding the dopamine transporter striatal signal. Second, the prolonged time to maximal striatal uptake necessitates imaging 14–24 hr after radiotracer injection for accurate quantitative studies. The ratio measure for $[^{123}I]$-β-CIT may be less reliable based on the very low background uptake determined after 1–2 half-lives of ^{123}I decay.

In this regard, the fluoropropyl derivative of $[^{123}I]$-β-CIT, designated $[^{123}I]$-FPCIT, has been shown to bind with greater affinity to the dopamine transporter (Ki = 3.5 nM) than to the 5-HT transporter (Ki = 9.73 nM) (14). However, the in vivo significance of a 2.8-fold greater affinity for the dopamine transporter is difficult to predict and is of the same magnitude as the relative difference of $[^{123}I]$-β-CIT for the dopamine transporter relative to the 5-HT transporter (2.4-fold). In preliminary healthy human studies with $[^{123}I]$-FPCIT (14–16), serial SPECT imaging shows rapid attainment of peak uptake

TABLE 1
Demographics

Patient no.	Age (yr)	Sex	Hoehn-Yahr stage	UPDRS		Medication
				Total	Motor	
PD 1	73	F	2.5	28	17	Selegeline 10 mg, Pramipexole 3 mg
PD 2	54	M	2	27.5	15.5	Pergolide 3 mg, Selegeline 5 mg
PD 3	79	F	1	21	11	None
PD 4	70	F	2	28	16	Selegeline 10 mg, Pergolide .75 mg
PD 5	58	M	1	24.5	15.5	Pergolide 1 mg
PD 6	69	M	1.5	24	13	Sinemet cR 200 mg, Amantidine 200 mg,
Mean	67					Pramipexole 3 mg
HS 1	48	F				
HS 2	83	M				
HS 3	52	M				
HS 4	79	F				
HS 5	75	M				
Mean	67					

HS = healthy subject; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

with relatively slow washout rates, suggesting the possibility of achieving a steady-state binding condition and using a simple ratio measure for quantitation of dopamine transporter density similar to $[^{123}I]$-β-CIT but much earlier after tracer injection.

The purpose of this study was to compare in a controlled, within-subject design $[^{123}I]$-β-CIT and $[^{123}I]$-FPCIT SPECT measures of dopamine transporters with the focus on plasma and brain kinetic characteristics of $[^{123}I]$-FPCIT striatal uptake with images taken serially over 6 hr.

MATERIALS AND METHODS

Radiopharmaceutical Preparation

High specific activity $[^{123}I]$-β-CIT was prepared from the corresponding trimethylstannyl precursor (1) (Research Biochemicals International, Natick, MA) and high radionuclidic purity $[^{123}I]$ NaI (Nordion International, Ltd., Vancouver, B.C., Canada) as described previously (11). Radiochemical purity was greater than 94% as measured with high-performance liquid chromatography (HPLC), and the specific activity was >5000 Ci/mmol.

Iodine-123-FPCIT was prepared from the trimethylstannyl precursor, producing a high specific activity (>5000 Ci/mmol) using a similar procedure to $[^{123}I]$-β-CIT as previously described (14). Radiochemical purity for $[^{123}I]$-FPCIT was greater than 95% determined by HPLC analysis.

Patients

Six Parkinson's disease patients (age 67.0 ± 9.7 yr, with these and subsequent measures expressed as mean ± s.d.) with idiopathic Parkinson's disease (Hoehn-Yahr Stages 1–3) were enrolled in the study after we had secured informed consent (Table 1). Inclusion criteria included age greater than 35 yr and at least two of the following: bradykinesia, resting tremor, rigidity, postural instability or freezing phenomenon (one of which is rest tremor or bradykinesia). All patients were evaluated in the Yale-New Haven Hospital General Clinical Research Center using the UPDRS and four timed motor tasks after 12-hr withdrawal from antiparkinson medications (17). Patients received their usual antiparkinson medication after the evaluation and during the SPECT study. They were excluded if they were taking medications known to have a direct effect on the dopamine transporter (e.g., benztropine). No changes in medications were permitted over the study duration. Patients received oral administration of supersaturated potassium iodide (SSKI, 800 mg) before each SPECT scan. Subjects participated in one SPECT study with each radiotracer separated by 7–21 days. The order of the radiotracer injections was randomized. Iodine-

123-FPCIT patients were imaged with serial 10-min acquisitions obtained from 1–6 hr postinjection.

Five healthy subjects (age 68.0 ± 14.6 yr) provided informed consent for the procedure and served as controls. The controls participated in the identical scan acquisition protocol on the same SPECT camera with $[^{123}I]$-FPCIT and $[^{123}I]$-β-CIT injected in a randomized fashion and separated by 7–21 days.

Image Acquisition and Analysis

Four fiducial markers each filled with 1–4 μCi $[^{99m}Tc]$ NaTcO$_4$ were attached to both sides of the head at the level of the canthomeatal line before imaging to facilitate posthoc reorientation of transaxial images. At 18–24 hr following the $[^{123}I]$-β-CIT injection, 120 raw projection images were acquired in a 128 × 128 matrix on the Picker Prism 3000XP camera (Picker International, Cleveland, OH). One 24-min acquisition was obtained.

Serial $[^{123}I]$-FPCIT SPECT scans were performed beginning 0.5–1 hr postinjection of the tracer and proceeding for 6 hr. Each acquisition was of 10-min duration, but otherwise used the same camera and acquisition parameters described above for $[^{123}I]$-β-CIT. Breaks of 45–90 min out of the camera were permitted over the course of the 6-hr study.

For both tracers, raw data were reconstructed from photopeak counts within a 20% symmetric energy window centered around 159 keV using a Butterworth prefilter (power factor = 10, cutoff = 1 cm) and a ramp filter reconstruction. Transaxial images were reoriented parallel to the canthomeatal plane and attenuation-corrected using Chang zero order correction (18) based on an ellipse fit to brain using a linear attenuation factor ($\mu = 0.12$ cm^{-1}) determined empirically from an ^{123}I-containing distributed source phantom.

The primary outcome measure was the ratio of specific striatal uptake to nondisplaceable uptake (designated V''_3) as described previously (5). For this ratio, eight contiguous transaxial slices (total thickness 2.8 cm) representing the most intense striatal uptake were summed. A standard region of interest (ROI) template was constructed based on coregistered MRI scans obtained from previous $[^{123}I]$-β-CIT studies in four controls. This template included ROIs for the left and right striatum, frontal cortex and occipital cortex. Small variations in individuals' brains required movement of the ROIs within the template without changing the individual ROI shape or pixel size. An additional ROI was placed in the midline on the axial slices in an area 3–4 slices inferior to the striatal slice in a region corresponding to highest activity in the

thalamus and midbrain structures noted on previous [123I]-β-CIT human studies. Data were expressed as cpm/voxel for each brain region. Estimates of specific striatal uptake were made by subtracting occipital cpm/pixel from total striatal cpm/voxel based on the low density of monoamine transporters in the occipital cortex. The ratio of striatal activity specifically bound to transporters divided by nondisplaceable activity is equal to the binding potential divided by the nonspecifically-bound compartment distribution volume (V_2) under conditions of equilibrium binding; i.e., when the concentration of parent compound is unchanging in plasma, receptor-bound and nonspecifically-bound brain compartments. Hence, this ratio, also designated V_3'', provides a measure linearly related to the density of dopamine transporters, but only when the tracer is in a condition of equilibrium binding (19). The quantitative validity of the ratio also assumes equivalence of nondisplaceable (or nonreceptor-bound) uptake in the striatum and occipital cortex. We derived V_3'' by dividing the operationally-defined specific striatal uptake by the occipital uptake, and this measure is equal to total striatal activity/occipital activity − 1.

For [123I]-β-CIT, the ratio was determined for ipsilateral and contralateral caudate and putamen, where contralateral is defined as the side opposite the side of initial symptom presentation in the Parkinson's disease patients and arbitrarily defined as the left in the control group. Two derived measures based on V_3'' ratios were calculated. These were the ratio of putamen to caudate for both the left and right striata and an asymmetry index (AI) defined as the absolute value of the right minus left striatal (caudate or putamen) region divided by the mean of the striatal regions and expressed as a percentage.

For the [123I]-FPCIT scans, the ratio of specific striatal uptake divided by occipital uptake (V_3'') was calculated for ipsilateral and contralateral caudate and putamen at each time point from 1−6 hr post-tracer injection. For each time point, the ratio of ipsilateral and contralateral putamen to caudate and an AI for caudate and putamen were calculated as described above for [123I]-β-CIT.

In addition, kinetic analysis of the rate of specific striatal washout was determined by fitting a linear regression to the data points obtained 4−6 hr post-tracer injection and expressed as a percent of change per hour. Comparison of washout rates was made between the Parkinson's disease patients and the controls for each striatal region (ipsilateral and contralateral caudate and putamen) and occipital cortex.

The mean ratio of V_3'' in Parkinson's disease patients and healthy control subjects was calculated for [123I]-β-CIT and at each time point from 3−6 hr postinjection for [123I]-β-FPCIT for all striatal regions. This ratio provides a general measure of the degree of reduction of the Parkinson's disease patients relative to the controls for each radioligand.

Pharmacokinetic and Metabolite Studies

Two controls and three Parkinson's disease patients had venous sampling every 30 min after injection of [123I]-FPCIT to determine plasma metabolites and assess the stability of the parent compound over time. This was performed by triple extraction of plasma in ethyl acetate and analytic HPLC using methods described previously (14). The percent of the sample representing the free (i.e., not protein-bound) parent compound was assayed by ultrafiltration through a 30,000 MW Centrifree (Amicon, Bedford, MA) filter (20). Similar to the analysis of brain time-activity data, the rate of elimination of total parent activity was calculated for the sampling time points 240−360 min postinjection of [123I]-FPCIT by a linear regression of the time-activity data. This method was used due to the close approximation of the data to a linear elimination during this phase of the study.

To further characterize the properties of radiometabolites of

[123I]-FPCIT, plasma and urine samples were extracted at different pH values. In one experiment with [123I]-FPCIT, the plasma samples remaining after extraction with ethyl acetate in the usual way were acidified (pH 1) with 1 M HCl and extracted again with 3 × ethyl acetate. A sample of urine (collected at 0−3 hr) was divided into three portions, and one was acidified to pH 1 with HCl, the second was made into a base of pH 10 with NaOH and the third was left untreated as a control (measured pH = 7). Measurement of pH was done with range 0−14 paper. Control experiments were performed by adding pure [123I]-FPCIT to samples of urine and blood and treating these samples in the same way. The extracts were dried and analyzed by HPLC. Standards of FPCIT, FPCIT acid, norCIT and FPCIT alcohol also were analyzed by HPLC, using ultraviolet detection at 254 nm using authentic samples of 2 β-carbomethoxy-3 β-(4-iodophenyl)tropane (norCIT), N-(3 fluoropropyl)−2 β-carbomethoxy-3 β-(4-iodophenyl)tropane (FPCIT), N-(3-fluoropropyl)−2 β carboxy-3 β-(4-iodophenyl) tropane (FPCIT acid) and N-(3-hydroxypropyl)−2 β-carbomethoxy-3 β (4-iodophenyl)tropane (FPCIT alcohol) obtained from Research Biochemicals International.

In separate experiments with two vervet monkeys and one baboon used for autoradiographic measurement of regional distribution of [123I]-β-CIT (3,13), animals were injected with 6−14 mCi radiotracer and killed 1.5−2.25 hr postinjection. Regional brain tissue samples (about 0.2 g each caudate, cortex and cerebellum) were minced and homogenized with 2 ml 0.12 M $HClO_4$ (Brinkmann Polytron, setting 6) for 10−20 sec while cooling in ice. A 1-ml aliquot was extracted with 3 × 1 ml ethyl acetate and the extract was evaporated to dryness, taken up in methanol and analyzed by HPLC as described for plasma. Recovery was determined in one experiment by adding an excess (about 5 μCi) of radiotracer to separate samples of cortex and cerebellum and processing in the same way; recovery was 90.1% and 91.7%, respectively.

Statistical Analysis

Statistical analyses were performed for each ligand, comparing differences in Parkinson's disease and control striatal ratios, putamen to caudate ratio and AI using nonparametric measures. In addition for [123I]-FPCIT serial data, a repeated measure (analysis of variance) of the count density determinations for striatum and occipital cortex was determined for scans acquired at 4−6 hr postinjection testing for time effects, group effects and group × time effects. Within-subject comparison of the mean V_3'' for [123I]-β-CIT ratios in Parkinson's disease patients and in healthy control subjects and of the mean [123I]-FPCIT V_3'' in Parkinson's disease patients and in controls was performed using nonparametric measures. In all instances, significance was assessed at the $p < 0.05$ level for the two-tailed tests.

RESULTS

Visual Comparison

Visual analysis of the [123I]-β-CIT and [123I]-FPCIT images demonstrated marked reduction in the striatal uptake in Parkinson's disease patients compared with the healthy control subjects. For both ligands, there was relatively greater loss in the posterior striatum corresponding to putamen (Fig. 1). Both radiotracers visually demonstrated significant left/right asymmetry of striatal uptake relative to the controls. The relative amount of cortical uptake was greater for [123I]-FPCIT compared with [123I]-β-CIT.

SPECT Measures

Ratios of specific to nondisplaceable uptake (V_3'' or total striatal uptake/occipital −1) are described in Table 2 for [123I]-β-CIT at 20 ± 2 hr postinjection and [123I]-FPCIT at 5 hr
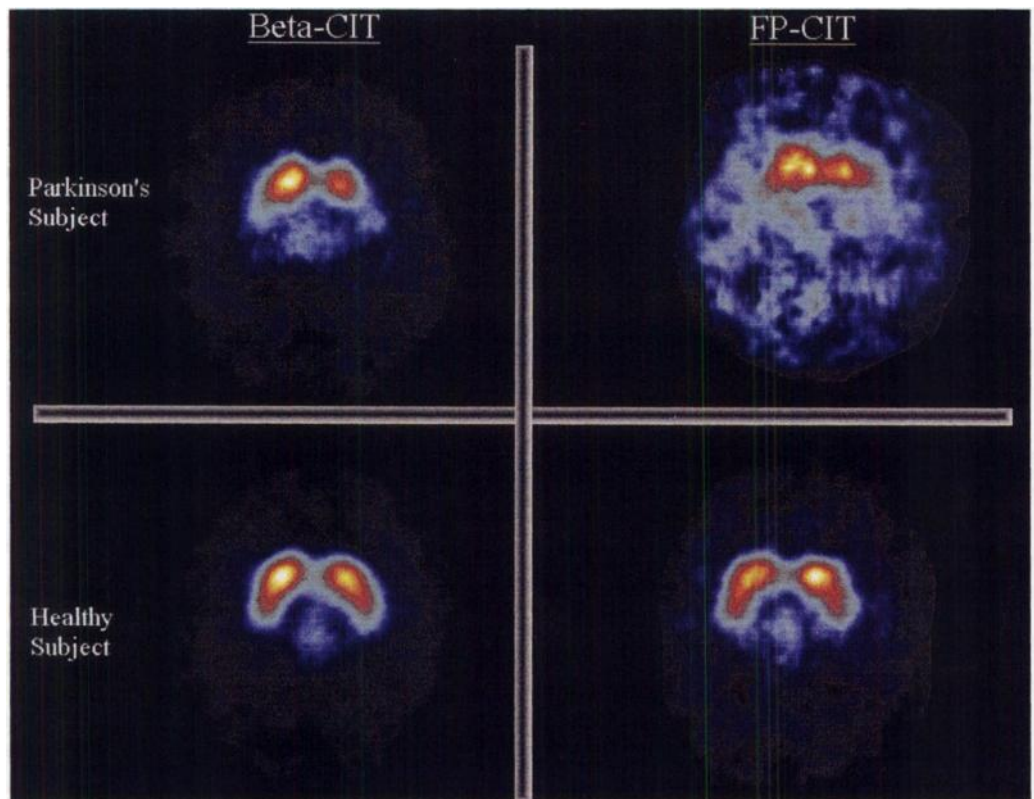
Parkinson's Subject

Healthy Subject

FIGURE 1. SPECT axial images in healthy control subject and Parkinson's disease patient after injection of 6 mCi [^{123}I]-β-CIT and in same subjects after injection of 9 mCi [^{123}I]-FPCIT. Both tracers show marked reductions in striatal uptake in Parkinson's disease patient with greater abnormality in putamen.

postinjection. Consistent with the visual assessments described above, both tracers demonstrated marked and significantly lower uptake striatal ratios in Parkinson's disease patients compared with the controls.

Specifically, for [^{123}I]-β-CIT striatal uptake ratios calculated for ipsilateral putamen (p = 0.008), contralateral caudate (p = 0.02) and putamen (p = 0.004) were all significantly different from the control values. Ipsilateral caudate (p = 0.25) was not significantly different between the Parkinson's disease patients and the healthy control subjects. In addition, ipsilateral, contralateral and mean striatal uptake ratios were all reduced significantly in Parkinson's disease patients compared with the controls (ipsilateral striatum p = 0.03, contralateral striatum p = 0.004, mean striatum p = 0.017). Comparison of the derived measures of the regional striatal uptake ratios AI showed no significant differences between the Parkinson's disease patients and the controls, while the putamen to caudate ratio showed a strong trend toward significant differences between the controls and the patients for the contralateral side (p = 0.052) and no significant differences in ipsilateral putamen to caudate ratios (p = 0.12).

Analysis of the 5-hr postinjection [^{123}I]-FPCIT data revealed that the Parkinson's disease patients' striatal uptake ratios were significantly different from the healthy control subjects' values calculated for ipsilateral caudate (p = 0.02) and putamen (p = 0.004) and contralateral caudate (p = 0.009) and putamen (p = 0.009). Ipsilateral, contralateral and mean striatal uptake were also all significantly different between Parkinson's disease patients and controls (p = 0.009, p = 0.004 and p = 0.004 for ipsilateral, contralateral and mean striatum, respectively). Iodine-123-FPCIT showed significant statistical discrimination between patients and controls for the AI in both caudate and putamen (p = 0.017 and p = 0.03, respectively), but it did not demonstrate significant differences in putamen to caudate uptake for either ipsilateral (p = 0.125) or contralateral sides (p = 0.082).

Comparing [^{123}I]-β-CIT and the 5-hr postinjection [^{123}I]-

FPCIT in Parkinson's disease patients, there were significant differences in the V''_3 uptake ratios for ipsilateral, contralateral and mean striatal uptake (p = 0.002, p = 0.002 and p = 0.002, respectively) reflecting the higher nondisplaceable (background) uptake for [^{123}I]-FPCIT. No significant differences were demonstrated in the AI for caudate (p = 0.48) and putamen (p = 0.59) or ipsilateral (p = 0.81) or contralateral (p = 0.59) putamen-to-caudate ratios between the two tracers in the Parkinson's disease group (Table 3). For the controls, there were only trends toward significant differences in the V''_3 uptake ratios for ipsilateral, contralateral and mean striatal uptake (p = 0.056, p = 0.095 and p = 0.056, respectively). Similar to the Parkinson's disease patients, the controls showed no significant differences in the AI for caudate (p = 0.42) and putamen (p = 0.69) or ipsilateral (p = 0.69) or contralateral (p = 0.42) putamen-to-caudate ratios between the two tracers. The mean striatal uptake ratios for [^{123}I]-FPCIT showed a nonsignificant trend toward increasing values going from the 3- to 6-hr time points in the controls but not in the Parkinson's disease patients.

The ratio of the mean striatal uptake values in Parkinson's disease patients to controls' values provides a measure of the reduction in the Parkinson's disease patients as a group relative to the controls. For [^{123}I]-β-CIT, the ipsilateral and contralateral ratios of Parkinson's disease to control were 0.57 and 0.46, respectively, with an overall Parkinson's disease-to-control ratio of 0.52. The Parkinson's disease-to-control ratios for [^{123}I]-FPCIT were lower than [^{123}I]-β-CIT with 6-hr ipsilateral and contralateral values of 0.41 and 0.31, respectively and an overall Parkinson's disease-to-control uptake ratio of 0.36. The values for [^{123}I]-FPCIT showed an initial time-dependence with lower, but stable, Parkinson's disease-to-control mean ratios on later postinjection scans (Fig. 2).

Analysis of the thalamus-to-midbrain V''_3 ratios demonstrated lower uptake ratios for [^{123}I]-FPCIT than [^{123}I]-β-CIT in both Parkinson's disease patients and healthy control subjects (Table 4). The overall ratio of [^{123}I]-FPCIT to [^{123}I]-β-CIT midbrain uptake was 0.35 for Parkinson's disease patients and 0.37 for

TABLE 2
Striatal Uptake Ratios

| Patient no. | [123I]-β-CIT striatal uptake ratios | | | | | | | [123I]-FPCIT striatal uptake ratios | | | | | | |
	Ipsilateral putamen	Ipsilateral caudate	Contralateral putamen	Contralateral caudate	Contralateral	Ipsilateral	Total	Ipsilateral putamen	Ipsilateral caudate	Contralateral putamen	Contralateral caudate	Contralateral	Ipsilateral	Total
PD 1	2.42	5.56	2.34	3.84	3.09	3.99	3.54	1.38	1.92	0.64	1.38	1.01	1.65	1.33
PD 2	4.52	6.86	2.85	5.14	4.00	5.69	4.84	1.45	3.00	1.06	1.76	1.41	2.23	1.82
PD 3	2.95	5.88	3.13	5.35	4.24	4.42	4.33	1.29	1.89	1.48	2.20	1.84	1.59	1.71
PD 4	1.23	3.68	1.24	3.73	2.49	2.45	2.47	0.54	1.04	0.35	1.12	0.74	0.79	0.76
PD 5	3.52	4.44	2.07	3.34	2.70	3.98	3.34	1.80	2.16	1.63	1.62	1.62	1.98	1.80
PD 6	2.66	2.81	1.81	2.08	1.95	2.74	2.34	0.77	1.21	0.65	0.80	0.72	0.99	0.86
Mean	2.88	4.87	2.24	3.91	3.08	3.88	3.48	1.21	1.87	0.97	1.48	1.22	1.54	1.38
COV	38%	31%	31%	31%	29%	30%	29%	39%	38%	53%	33%	38%	36%	34%
HS 1	7.20	9.58	8.24	8.08	8.16	8.39	8.27	4.14	5.83	4.88	5.49	5.18	4.98	5.08
HS 2	5.65	6.83	5.63	6.96	6.29	6.24	6.27	3.23	4.63	3.01	4.34	3.68	3.93	3.80
HS 3	9.73	10.34	8.67	10.17	9.42	10.04	9.73	5.44	5.92	4.84	6.36	5.60	5.68	5.64
HS 4	5.03	5.47	4.52	5.41	4.97	5.25	5.11	1.89	2.17	1.97	1.93	1.95	2.03	1.99
HS 5	3.87	4.15	3.85	4.62	4.24	4.01	4.12	2.13	2.87	2.08	2.47	2.27	2.50	2.38
Mean	6.30	7.27	6.18	7.05	6.62	6.79	6.70	3.37	4.28	3.35	4.12	3.74	3.82	3.78
COV	36%	36%	35%	31%	33%	36%	34%	44%	40%	43%	46%	44%	41%	42%

COV = coefficient of variation; HS = healthy subject; PD = Parkinson's disease.

controls. Differences between the midbrain uptake ratios for the two tracers were significant when the Parkinson's disease patients and controls were combined (p = 0.002), but only bordered on statistical significance (p = 0.06) when groups were analyzed individually, consistent with the expected lower thalamic-to-midbrain uptake [123I]-FPCIT. Thalamus-to-midbrain uptake (decay-corrected cpm/voxel normalized to administered dose) for [123I]-FPCIT were above the cortical background (p = 0.002), suggesting some signal in this region could be related to the 5-HT transporter binding.

Iodine-123-FPCIT Striatal and Occipital Washout

Analysis of time-activity data for specific striatal and occipital uptake showed elimination of brain activity between the 240–360-min postinjection time points (Fig. 3). Table 5 summarizes the brain percent washout per hour for uptake in the healthy control subjects and the Parkinson's disease patients. Mean striatal washout rates were 4.9% and 8.2% per hour for the striatum (controls and Parkinson's disease patients, respectively) and 4.8% and 5.4% per hour for the occipital cortex (controls and Parkinson's disease patients, respectively). There were no significant within-group or between-group differences for [123I]-FPCIT washout in occipital, ipsilateral, contralateral or mean striatal regions.

Iodine-123-FPCIT Plasma Analysis

Elimination of the total parent compound from the venous plasma was assessed for venous samples obtained from 240–360 min postinjection of [123I]-FPCIT in three Parkinson's disease patients and two controls by linear regression. For the Parkinson's disease patients, plasma elimination was 12.6% ± 4.7%/hr and for the controls 19.6% ± 1.4%/hr. Low subject numbers precluded meaningful statistical comparison of the two groups.

Characterization of Iodine-123-FPCIT Metabolites

The ethyl acetate extractable fraction of radioactivity in plasma went from 70.5% at 30 min postinjection to 32.3% after 6 hr. However, of the remaining, unextracted, radioactivity remaining in the aqueous phase, roughly the same fraction (78.2%–85.4%), was extracted after adjusting to pH 1 from samples at all time points. HPLC of the acid extract showed the radioactivity to elute near the void volume similar to authentic FPCIT acid. A 3-hr urine sample extracted 87.3% at pH 1, 37.5% at pH 7 and 26.4% at pH 10. Control [123I]-FPCIT added to the urine gave extractions of 98.9, 98.8 and 93.7% at the same pH values. A 6-hr plasma sample extracted 85.3% at pH 1 and 29.1% at pH 7. HPLC of the extracted activity from the urine and plasma showed peaks at the same retention time as the parent [123I]-FPCIT and of FPCIT acid. No clear radioactive peaks were detected at the retention times of norCIT or FPCIT alcohol. A peak was observed earlier than the parent, but its retention time did not match that of any of the standards.

DISCUSSION

These data show that both [123I]-FPCIT and [123I]-β-CIT striatal uptake was reduced in Parkinson's disease patients compared with age-matched healthy control subjects. Corroborating earlier reports of [123I]-β-CIT in Parkinson's disease patients and controls, both tracers showed that Parkinson's disease patients have the greatest reductions in the putamen contralateral to the side of symptom onset consistent with postmortem assessments of alterations in striatal dopamine transporter density in idiopathic Parkinson's disease patients. Further, the radiotracers showed greater reductions in putamen relative to caudate and greater left/right asymmetry of uptake in the Parkinson's disease patients than in the controls.

TABLE 3
Striatal Asymmetry and Putamen-to-Caudate Ratios

Patient no.	[^{123}I]-β-CIT				[^{123}I]-FPCIT			
	Asymmetry index		Putamen-to-caudate		Asymmetry index		Putamen-to-caudate	
	Caudate	Putamen	Ipsilateral	Contralateral	Caudate	Putamen	Ipsilateral	Contralateral
PD 1	37%	4%	0.44	0.61	33%	74%	0.46	0.72
PD 2	29%	45%	0.66	0.55	52%	31%	0.60	0.48
PD 3	10%	6%	0.50	0.59	15%	14%	0.67	0.68
PD 4	1%	1%	0.33	0.33	8%	43%	0.31	0.52
PD 5	28%	52%	0.79	0.62	28%	10%	1.01	0.84
PD 6	30%	38%	0.95	0.87	42%	17%	0.81	0.64
Mean	22%	24%	0.61	0.60	30%	32%	0.65	0.65
COV	61%	95%	38%	29%	56%	76%	38%	20%
HS 1	17%	13%	0.75	1.02	6%	16%	0.89	0.71
HS 2	2%	0%	0.83	0.81	6%	7%	0.69	0.70
HS 3	2%	12%	0.94	0.85	7%	12%	0.76	0.92
HS 4	1%	11%	0.92	0.84	12%	4%	1.02	0.87
HS 5	11%	0%	0.93	0.83	15%	2%	0.84	0.74
Mean	6%	7%	0.87	0.87	9%	8%	0.84	0.79
COV	111%	87%	9%	10%	42%	67%	15%	13%

COV = coefficient of variation; HS = healthy subject; PD = Parkinson's disease.

The critical finding in this study was that [^{123}I]-FPCIT showed relatively greater differences in striatal uptake ratios in Parkinson's disease patients relative to the controls than [^{123}I]-β-CIT. This could be due to either overestimation of dopamine transporter density in controls by [^{123}I]-FPCIT or overestimation of the dopamine transporter in Parkinson's disease patients by [^{123}I]-β-CIT. The latter would arise in circumstances of a significant 5-HT transporter signal in the striatum in Parkinson's disease patients. Several lines of evidence argue against this possibility. First, in a baboon model, intravenous administration of the 5-HT transporter agent citalopram during dynamic [^{123}I]-β-CIT SPECT imaging has no effect on the striatal time-activity curve while decreasing activity in the midbrain regions known to have a high density of 5-HT transporters (3). Second, treatment studies in humans with citalopram (21) have no effect on striatal binding ratios [^{123}I]-β-CIT. Further, post-

mortem data suggests there is a significant reduction of 5-HT transporters in the striatum in patients with idiopathic Parkinson's disease, suggesting the limited availability of binding sites for 5-HT transporters in the target region may parallel the dopamine transporter reductions in the disorder (22).

Some authors have suggested that suggested that the presence of a lipophilic metabolite of [^{123}I]-β-CIT may confound the validity of the simple ratio measurement for providing accurate information about the density of dopamine transporters (23–26). Could the production of such a metabolite of [^{123}I]-β-CIT be responsible for the different estimates of dopamine transporter density in the Parkinson's disease patients relative to the controls for the two radiotracers? This seems an implausible explanation in that there would have to be an assumption of systematic patient and control differences in the metabolism of [^{123}I]-β-CIT. Indeed, chemical analysis of a monkey brain after administration of [^{123}I]-β-CIT showed that >85% of the tissue activity was unchanged from the parent compound. In addition,

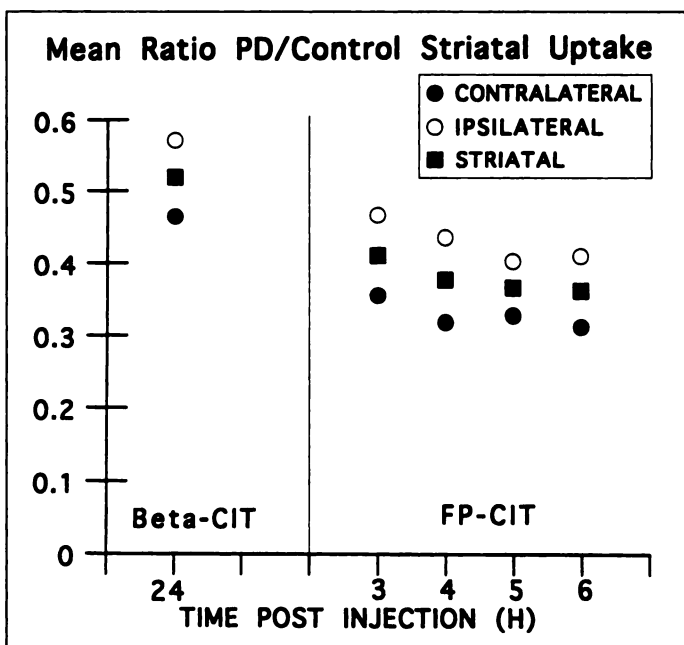**FIGURE 2.** Time-dependency of mean Parkinson's disease-to-control [^{123}I]-FPCIT striatal uptake values.

TABLE 4
Midbrain Uptake Ratios

Patient no.	Midbrain ratios		FPCIT-to-β-CIT ratio
	β-CIT	FPCIT	
PD 1	1.49	0.58	0.39
PD 2	2.40	0.91	0.38
PD 3	2.46	0.95	0.39
PD 4	1.75	0.39	0.22
PD 5	1.04	0.36	0.35
PD 6	1.57	0.57	0.36
Mean	1.78	0.63	0.35
COV	31%	40%	18%
HS 1	3.21	1.24	0.39
HS 2	2.03	0.57	0.28
HS 3	3.67	1.67	0.45
HS 4	1.32	0.45	0.34
HS 5	1.43	0.59	0.41
Mean	2.33	0.90	0.37
COV	45%	58%	18%

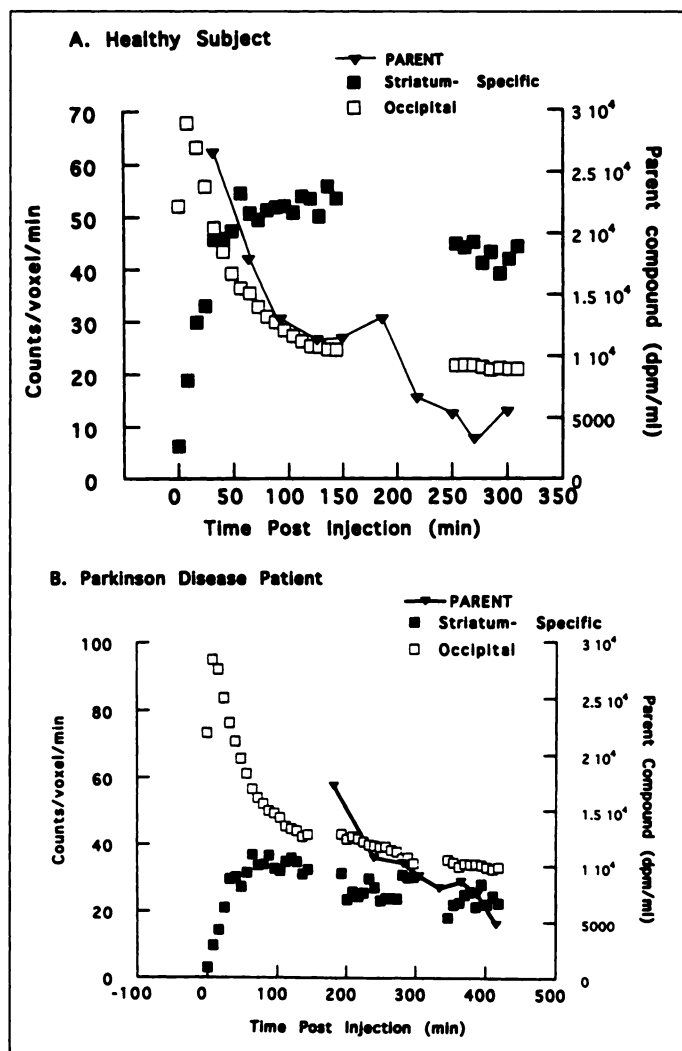COV = coefficient of variation; HS = healthy subject; PD = Parkinson's disease.

FIGURE 3. Time-activity data for [^{123}I]-FPCIT brain uptake and parent plasma activity in (A) representative healthy subject and (B) Parkinson's disease patient. They represent extremes of range of washouts in study.

the lipophilic metabolite most likely represents the free acid with low potency for the dopamine transporter. Differences in the analytic methods may be responsible for the apparent differences in the characterization of the radiometabolites of

[^{123}I]-β-CIT. The ethyl acetate extraction/HPLC analysis method used in these studies gives a two-stage separation—an initial, gross, separation into an ethyl acetate extractable fraction and a nonextractable fraction, which we have previously termed the "lipophilic" and "polar" fractions (13). HPLC analysis of the "lipophilic" fraction gives definite identification and quantification of the parent tracer. Other investigators have used solvent denaturation and direct HPLC injection of the supernatant solution (24,27,28), in which case the components eluting, at the earliest times, on reversed phase HPLC are termed "polar" and those eluting later are termed "lipophilic," even though all of them would be classified as lipophilic since they are de facto soluble in organic solvent.

The results of this study support the hypothesis that the major metabolite of [^{123}I]-β-FPCIT is the carboxylic acid (FP acid). At physiological pH, this material should be largely ionized (expected pKa about 4.5, thus > 99% undissociated at pH 7.4) and is not extracted. Acidifying to pH 1 allowed about 80% of the remaining activity (90%–94% cumulative) to be extracted, and HPLC of the extract coincided with the acid. The remaining unextractable activity (6%–10%) may be truly polar metabolites such as sodium iodide or the glucuronide conjugate of the acid or hydroxylated metabolites. This conclusion is consistent with results from other studies (24,26,29). The relative proportions of parent, acid, polar and unknown metabolites are remarkably similar. It is also likely that the unknown component we observed is the same one reported by Bergstrom et al. (25), since it elutes at the same relative retention time in the same HPLC system. Its extraction properties are similar to that of [^{123}I]-FPCIT and [^{123}I]-β-CIT; at pH 7 it is extracted by ethyl acetate. It elutes somewhat earlier than the parent FPCIT in a basic mobile phase, but is not separated in an acidic mobile phase. It is probably not acidic since its extraction is not affected by pH. It is not the alcohol resulting from solvolysis/defluorination. Some speculation as to its nature might be: N-oxide, phenolic metabolite; 2a-epimer. Consequences for the interpretation of [^{123}I]-β-FPCIT and [^{123}I]-β-CIT scans are encouraging; the major metabolite, CIT acid, is known to have low dopamine transporter affinity (474 nM; Carroll FI, personal communication, 1996) and does not penetrate the brain (28). We confirmed these assumptions by an analysis of the radioactivity in the caudate, cortex and cerebellum of two vervets and one baboon studied approximately 2 hr postinjection, at a

TABLE 5
Iodine-123-FPCIT Striatal Washout

Patient no.	[^{123}I]-FPCIT elimination (%/hr) striatum				Plasma parent compound
	Occipital	Contralateral	Ipsilateral	Mean	
PD 1	7.2	20.7	13.9	16.7	
PD 2	6.1	-3.9	1.2	-0.7	
PD 3	4.5	11.7	6.2	9.3	
PD 4	4.6	13.7	12.5	12.6	14.6
PD 5	4.7	9.7	5.7	7.1	7.2
PD 6	5.6	-0.5	6.6	4.3	15.9
Mean	5.4	8.6	7.7	8.2	12.6
COV	0.2	1.1	0.6	0.7	0.4
HS 1	7.0	1.4	2.3	1.8	
HS 2	5.5	3.1	5.5	4.3	
HS 3	7.2	3.0	4.4	3.7	
HS 4	4.6	7.1	0.2	6.2	20.6
HS 5	-0.2	8.2	8.9	8.6	18.7
Mean	4.8	4.6	4.3	4.9	19.7
COV	0.6	0.6	0.8	0.5	0.1

COV = coefficient of variation; HS = healthy subject; PD = Parkinson's disease.

time when the plasma consisted of 12%–35% parent compound. Greater than 90% of brain radioactivity was extractable by ethyl acetate in all tissues, and analysis by HPLC revealed that 82%–100% of the activity was the parent compound.

Considering the possibility of overestimation of dopamine transporter density in controls with [^{123}I]-FPCIT SPECT as an explanation for the differences in the two tracers, analysis of plasma parent compound, SPECT occipital activity and SPECT specific striatal activity indicates a rate of washout of 15.4%, 5.2% and 6.7% per hour from patients and controls, respectively. This is approximately 15- to 20-fold faster than comparable data with [^{123}I]-β-CIT in humans (5,6). As indicated earlier, the quantitative validity of the simple ratio of striatal to background brain region depends on the achievement of steady levels of activity in these regions. Under conditions deviating from this, such as those produced during a so-called transient equilibrium when elimination rates of target and background regions may parallel each other and produce a stable target-to-background ratio, Carson et al. (30) have demonstrated the simple ratio overestimates receptor density. This overestimation is related to the number of receptors in the target region with regions of higher receptor density producing greater overestimates of density. Hence, applying this analysis to the present data, the differences between [^{123}I]-β-CIT and [^{123}I]-FPCIT with regard to estimation of dopamine transporter density in Parkinson's disease patients relative to controls may be explained by the faster rate of elimination of the parent compound from the plasma and brain for [^{123}I]-FPCIT. Previous estimates of the magnitude of this error have been published for [^{123}I]-β-CIT SPECT ratio measure (5). In summary, while much interest has been directed to describing the uptake phase for dopamine transporter ligands, the characteristics of the brain elimination phase are critical to validity of the dopamine transporter density measurements when simple ratios are used. In the absence of kinetic modeling of ligands with significant specific washout, ratios need to be considered suspect measures of dopamine transporter density. Other methods of correcting for this include characterization of the peak uptake ratio using the method of Farde et al. (31) or administration of the radiotracer as a continuous infusion (equilibrium method).

The rapid rate of plasma washout of parent [^{123}I]-FPCIT (15.4%/hr) for relative to nonspecific brain compartment (5.2%/hr) could be explained by the presence of a metabolite in the extractable fraction. This speculation must be tempered by two considerations. First, the relative differences in these washout rates is suspect given the low number of subjects and Parkinson's disease patients (n = 6 total) with plasma analyses, and second, there has been inadequate characterization of the this fraction at present.

The low patient and control numbers in this study do not permit us to address the issue of which tracer is better from a diagnostic perspective. The greater differences exhibited between patients and healthy control subjects for [^{123}I]-FPCIT compared with [^{123}I]-β-CIT, while not quantitatively valid measures of dopamine transporters, may be useful for purposes of differential diagnosis in clinical settings where the question of distinguishing idiopathic Parkinson's disease or parkinsonism from normal aging or essential tremor would be at issue. Larger studies with [^{123}I]-FPCIT would be necessary to achieve a comparable level of confidence in the overall validity and generalizability of this tracer as a clinical tool.

Several potential sources of error in this analysis need to be considered. First, patients were medicated during the scans, although they were excluded from participation if taking drugs that directly affected the dopamine transporter, and no alter-

ations in the treatment regimen were permitted during the study. Nonetheless, two patients were treated with selegeline, whose metabolite has amphetamine properties that may have weak potency at the dopamine transporter. Careful, within-subject, evaluation of the medication effect would be useful for further studies with dopamine transporter radiotracers. Second, there were an unexpected absence of statistically significant differences in this study for the derived measures of asymmetry and putamen to caudate ratio that have been shown to be altered significantly in Parkinson's disease patients relative to controls (7). This is most likely due to the small group numbers in our study compared with previous ones.

CONCLUSION

In summary, the major conclusions of this study are:

1. The nonspecific uptake of [^{123}I]-FPCIT was greater than [^{123}I]-β-CIT causing [^{123}I]-FPCIT to have a lower ratio of specific to nondisplaceable striatal uptake (V''_3).
2. The thalamic/midbrain uptake of [^{123}I]-β-CIT was higher than [^{123}I]-FPCIT and [^{123}I]-FPCIT thalamic/midbrain ratios were higher than cortical background, which probably reflected binding at the 5-HT transporters.
3. While the striatal and occipital activity of [^{123}I]-β-CIT had been previously shown to be very stable over the period 18–27 hr postinjection (less than 1%/hr), the striatal and occipital uptake of [^{123}I]-FPCIT showed significant washout in the period 3–6 hr postinjection (5%–8%/hr). This was corroborated by plasma analysis of the elimination of [^{123}I]-FPCIT showing elimination rates of 13%–20%/hr.
4. The striatal V''_3 values of [^{123}I]-FPCIT gradually increased and then became stable during the 3–6 hr postinjection, and the differences between the healthy control subjects and the Parkinson's disease patients were greater with [^{123}I]-FPCIT than with [^{123}I]-β-CIT. This is consistent with the faster brain washout of [^{123}I]-FPCIT and the resultant transient equilibrium state.
5. Measured in the same group, the statistical significance of reduced striatal uptake of [^{123}I]-FPCIT in Parkinson's disease was very similar to [^{123}I]-β-CIT. However, the decreased striatal uptake of [^{123}I]-FPCIT relative to [^{123}I]-β-CIT was of greater magnitude in the Parkinson's disease group (37%) than in the control group (52%) again suggesting the achievement of transient equilibrium binding conditions, which the modeling theory predicted would result in an overestimation of dopamine transporter density by [^{123}I]-FPCIT in healthy subjects.
6. Characterization of [^{123}I]-FPCIT radiometabolites suggested, similar to [^{123}I]-β-CIT, that the primary metabolite is the carboxylic acid.

Finally, [^{123}I]-FPCIT SPECT is sensitive to reductions in striatal uptake in Parkinson's disease patients, and it may provide useful data for clinical diagnostic purposes. Nonetheless, for studies requiring absolute quantitation, as in the evaluation of Parkinson's disease progression, [^{123}I]-FPCIT SPECT may not provide accurate quantitation of dopamine transporters.

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Discordance of Technetium-99m-HMPAO and Technetium-99m-ECD SPECT in Herpes Simplex Encephalitis

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Technetium-99m-hexamethyl propyleneamine oxime (HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (ECD) accumulate in brain tissue in proportion to regional cerebral blood flow in healthy subjects and in patients with a variety of neurological diseases. We report on four patients with herpes simplex encephalitis and the discordance between these two approved cerebral perfusion imaging radiopharmaceuticals. **Conclusion:** SPECT images showed unilateral regional increase of ^{99m}Tc-HMPAO uptake and decrease of ^{99m}Tc-ECD uptake in the affected temporal lobe.

Key Words: SPECT; technetium-99m-hexamethyl propyleneamine oxime; technetium-99m-ethyl cysteinate dimer; herpes simplex encephalitis

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After intravenous administration, ^{99m}Tc-hexamethyl propylene-amine oxime (HMPAO; Ceretec; Amersham, United Kingdom) and N,N'−1,2-ethylene-diylbis-L-cysteine diethyl ester (ECD;