Clinical Significance of F-18 FP-CIT Dual Time Point PET Imaging in Idiopathic Parkinson's Disease

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Abstract

Purpose The purpose of this study was to investigate the diagnostic value of dual time point F-18 FP-CIT PET imaging in idiopathic Parkinson's disease (PD).

Materials and Methods Twenty-four patients with PD (mean age 69.6) and 18 healthy people (mean age 70.26) underwent two sequential PET/CT scans (dual time point imaging) at 90 and 210 min after F-18 FP-CIT injection. Tracer activity of region of interest was measured in the caudate, putamen and a reference region in the brain from both time points. The outcome parameter was the striatooccipital ratio (SOR). Normal SOR values were obtained in the control group. The percent change in tracer activity between 90- and 210-min images was calculated. The SOR values and the percent change in tracer activity were compared between the patients and healthy control group.

Results The SOR values for the caudate, anterior and posterior putamen at both 90- and 210-min images were significantly reduced in the patients with PD. The lowest P value was obtained for the anterior and posterior putamen ($p < 0.001$) at both time points. There were significant differences of the percent change in tracer activity for the anterior and posterior putamen in the two groups ($p = 0.01$). **Conclusions** F-18 FP-CIT PET scans at 90 and 210 min after injection are both able to diagnose PD. Therefore, the 90-min image by itself is sufficient for diagnosing PD.

Keywords F-18 FP-CIT PET · Dual time point · Parkinson's disease

Introduction

Loss of dopaminergic neurons in the substantia nigra is a characteristic feature of Parkinson's disease (PD). This neuronal loss is more severe in the ventrolateral nigra, projecting mainly to the posterior putamen. Dopaminergic dysfunction in PD has been visualized with positron emission tomography (PET) or single photon emission tomography (SPECT) by using various tracers [1–5].

Many radiotracers targeting the dopamine transporter, such as I-123 beta-CIT, I-123 FP-CIT, Tc-99m TRODAT and F-18/C-11 CFT, were developed, but few of these have been used in clinical practice. However, fluorinated N-3-fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl) nortropane (F-18 FP-CIT) was recently approved by the Korean Food and Drug Administration for diagnosing PD after clinical trial and is widely used in clinical practice.

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For clinical use of F-18 FP-CIT in PD, many researchers have studied the pharmacokinetics of the radiotracer and image acquisition times [5–7]. The specific striatal uptake of F-18 FP-CIT was found to reach its maximal value at 90–120 min postinjection in normal subjects on dynamic analysis [5, 6]. However, Kim [8] insisted more research was needed for choosing the image acquisition time because the specific striatal uptake of F-18 FP-CIT was not reached in this time in some of patients but could reach a pseudoequilibrium state after 2 h like I-123 FP-CIT.

To the best of our knowledge, a study to determine the appropriate imaging time for F-18 FP-CIT PET/CT in clinical practice has not been reported in the literature.

The aim of our study was to select the appropriate imaging time using F-18 FP-CIT dual point PET/CT imaging for the diagnosis of PD.

Materials and Methods

The study protocol was approved by our institutional ethics committee, and informed consent was obtained in all cases.

Subjects

All the subjects were prospectively recruited, and the study was conducted between June 2009 and March 2010. We recruited 24 consecutive patients (male:female=6:18, 69.7 ±6.2 years, Hoehn and Yahr grade=2.33±0.9) with PD and 18 age-matched healthy controls (Table 1). All of the patients with PD were examined in the Movement Disorder Clinic and Dementia Clinic of Incheon St. Mary's Hospital. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria.

We excluded patients with cognitive impairment; secondary causes of parkinsonism, e.g., Wilson's disease; neuroleptic drug use or psychiatric diseases that would, in the investigator's judgment, interfere with the safe conduct of the study; those who had clinical signs compatible with atypical parkinsonism, such as multiple system atrophy; progressive supranuclear palsy and cortical-basal degeneration; and those who fulfilled the DSM-IV criteria for delirium or amnesic and depressive disorder. PD patients with a cerebrovascular disease or focal neurological signs of cerebral disease were also excluded.

Table 1 Demographic data and general cognitive function test results

Variables	PD	Control	<i>p</i> value
Number of subjects	24	18	-
Gender, male/female	6/18	7/11	0.8
Mean age, years	69.7±6.2	70.3±10.2	0.3
Mean duration of PD, months	22.3±10.2	-	-
Hoehn-Yahr stage	2.3±0.9	-	-

PD: idiopathic Parkinson's disease

F-18 FP-CIP PET/CT

Patients were allowed to continue antiparkinson medication, but the drugs that could reduce specific to nonspecific striatal binding, such as d-amphetamine, methylphenidate, benzatropine, bupropion, cocaine, mazindol and phentermine, were restricted before the exam. Subjects were given 149–259 MBq of F-18 FP-CIT (3.7 MBq/kg) intravenously. Two sequential PET/CT scans (dual time point) were acquired 90 and 210 min after the F-18 FP-CIT injection with the subject's eyes closed using Discovery STE (GE Healthcare, Milwaukee, WI, USA). The data were acquired in 3D mode. CT scanning began at the vertex and progressed to the skull base (30 mAs; 140 kVp; slice 3.75 mm), and PET imaging followed immediately over the same region with 15-min duration. The CT data were used for attenuation correction, and images were reconstructed using the standard ordered subset expectation maximization (OSEM 2 iterations, 8 subsets) algorithm.

Image Analysis

An experienced nuclear medicine physician reviewed early and delayed PET/CT images at a workstation (Advantage Workstation version 4.3, GE Healthcare, Milwaukee, WI, USA). A standard set of regions of interest (ROIs) was used to sample the average standardized uptake value (SUVavg) of both the caudate and putamen, and a nonspecific reference region in the occipital cortex at the sum images of two or three transverse planes. The putamen was divided into anterior and posterior halves along its longitudinal axis. Ratios of specific to non-specific binding (SOR) were calculated by dividing the striatal count density by the occipital count density. Furthermore, the percent change in the uptake value between early and delayed images was calculated. The percent change in the uptake value was defined as:

$$\frac{(\text{SUVavg of striatum on 210 min image} - \text{SUVavg of striatum on 90 min image})}{\text{SUVavg of striatum on 90 min image}} \times 100(\%)$$

Table 2 SOR of FP-CIT PET/CT in patients affected by Parkinson's disease and healthy subjects

Location	PD (n=24)	Control (n=18)	<i>p</i> value
90-min caudate nucleus	3.79±0.8	4.48±1.51	0.001
90-min anterior putamen	3.58±0.91	4.98±0.72	<0.001
90-min posterior putamen	2.82±1.05	5.03±0.72	<0.001
210-min caudate nucleus	4.79±1.56	6.11±0.99	0.006
210-min anterior putamen	4.34±1.65	6.43±0.86	<0.001
210-min posterior putamen	3.24±1.73	6.34±0.89	<0.001

SOR: striatooccipital uptake ratio, PD: idiopathic Parkinson's disease

Statistical analysis

All semiquantitative data were expressed as mean ± SD. FP-CIT uptake values were compared between the patients and the control group using the Mann-Whitney test. Statistical significance was assumed at the 5% level. The statistical analyses were performed using the SPSS software version 17.0 package.

Fig. 1 a–d Images of F-18 FP-CIT uptake at the level of the striatum in a healthy control (a and b), Parkinson's disease patient (c and d) at 90- and 210-min image, respectively. The SOR values for the caudate, anterior and posterior putamen at both 90- and 210-min images were significantly reduced in the patients compared with the control group

Results

Uptake Values

Striatal F-18 FP-CIT uptake values on 90- and 210-min images are summarized in Table 2.

The SOR of the caudate nucleus, anterior and posterior putamen is 3.79±0.8, 3.58±0.91 and 2.82±1.05 on the patients' 90-min images and 4.79±1.56, 4.34±1.65 and 3.24±1.73 on the patients' 210-min images. The SOR values for the caudate, anterior and posterior putamen at both 90- and 210-min images were significantly reduced in the patients compared with the control group (Fig. 1). The lowest *p* value was obtained for the anterior and posterior putamen (*p*<0.001) at both time points.

The striatal uptake was reduced on the delayed images in both groups (Fig. 2). Anterior and posterior putaminal uptake was significantly diminished on the delayed images in the patients (*p*=0.01) (Table 3).

Normal Aging

No significant effect of aging was found for the striatal uptake value of F-18 FP-CIT (*p*=0.34 for the mean

Fig. 2 a–c Changes of SUVavg on 90- and 210-min images of FP-CIT PET/CT scans in the patients with Parkinson's disease and healthy controls. The striatal uptake was reduced in the delayed images in both groups. No significant difference in the change of caudate activity (**a**) was noted between the patients and control group ($p=0.57$), whereas anterior (**b**) and posterior (**c**) putaminal uptake was significantly diminished in the patients ($p=0.01$)

Table 3 The percent change in the tracer activity in patients affected by Parkinson's disease and healthy subjects

Location	PD (n=24)	Control (n=18)	<i>p</i> value
Caudate nucleus	-7.57±14.7 %	-6.4±10.2 %	0.57
Anterior putamen	-14.36±13.2 %	-6.2±7.8 %	0.01
Posterior putamen	-19.7±15.7 %	-8.5±7.0 %	0.01

PD: idiopathic Parkinson's disease

caudate, $p=0.81$ for the mean putamen) in the healthy control group.

Discussion

The value of dual point PET imaging using F-18 FDG has been widely studied with emphasis on differentiation of benign and malignant tumors and improvement of tumor detection in the oncology area based on the alteration of glucose-6-phosphatase expression [9–11].

Specific uptake of F-18 FP-CIT of the normal striatum reaches a peak equilibrium state at 90 min or more after injection [5, 6]. In Parkinson patients, however, it is thought that the time required to reach this peak equilibrium state is shortened [5], and F-18 FP-CIT activity is likely to washout sooner. Under this assumption, the diagnostic value of a delayed image was evaluated in this study with dual point F-18 FP-CIT PET/CT.

The authors obtained early images 90 min after injection because several studies showed that specific uptake into the corpus striatum peaks after at least 90 min post-administration in healthy controls [5, 6]. However, not all patients achieve a peak equilibrium state at 90–120 min, and pseudoequilibrium is estimated to occur more than 2 h later. Therefore, Kim et al. [8] recommended the same injection-to-imaging time as I-123 FP-CIT SPECT for F-18 FP-CIT PET/CT because the I-123 FP-CIT and F-18 FP-CIT share similar pharmacokinetics. Since images were taken 3–6 h post-injection for the I-123 FP-CIT SPECT [12], delayed images were acquired 210 min after injection in the present study.

Initially, it was presumed that a delayed image might show superior diagnostic value because of better contrast of radioactivity caused by selective loss of putaminal uptake, but there was no problem in diagnosing PD by the 90-min image alone. Therefore, acquisition of only a 90-min image is sufficient for diagnosis and can reduce radiation exposure and imaging time.

Although there was no added diagnostic benefit of a delayed F-18 FP-CIT PET/CT image, the dual point PET/CT image showed a higher percent change of striatal uptake value in PD.

The authors naturally anticipated a significant decline in the SOR in delayed images. However, because the occipital uptake in the delayed image decreased even more than the striatum, which demonstrated a significantly reduced SUVavg, the SOR showed a statistically insignificant change.

Further study is expected to see if there is a correlation between the percent change of striatal activity in PD, and disease severity and prognosis in a larger population.

Previous studies have mentioned an aging effect on striatal DAT binding. Eshuis et al. [13] reported a significant age-dependent decline in the SOR of FP-CIT of 3.9% per decade in healthy controls. A study using beta-CIT SPECT showed a reduction in striatal binding of 6.6% per decade [14]; another SPECT study using Tc-99m TRODAT demonstrated a decline of 6.2% per decade [15]. In a post-mortem study [16], a decay of 4.7% per decade of pigmented neurons in the substantia nigra was demonstrated. However, in our data, striatal FP-CIT uptake did not change with age ($p=0.34, 0.81$), which is thought to be because of the small number of participating healthy controls.

Park et al. [17] reported that SOR was 3.1 ± 0.6 for the caudate nucleus and 3.2 ± 0.7 for the putamen on 90-min FP-CIT PET imaging, whereas SOR was 4.48 ± 1.51 for the caudate nucleus, 4.98 ± 0.72 for the anterior putamen and 5.03 ± 0.72 for the posterior putamen in this study. A relatively higher uptake value in our study is probably due to a difference in the average age of the control group (72 ± 6.0 vs. 70.3 ± 10.2) and dose of the radiotracer [fixed dose of 185 MBq vs. 149–259 MBq (3.7 MBq/kg)] between the two studies. To compare different studies on the uptake value of FP-CIT is difficult since the patient populations (early vs. advanced), the way of calculating the uptake ratio and the time of imaging vary between the studies.

Figure 2 shows considerable overlapping of striatal uptake values between the patients with PD and healthy controls. We hypothesize that these results may be due to an aging effect on striatal uptake, although the aging effect in the control group was not statistically significant.

There are some limitations to our study. First, a relatively small number of patients and healthy controls were included in the study, so our study could not detect any age effect. If only 90-min images are used for diagnosis of PD, normal striatal uptake can be underestimated, but this fact will not cause difficulty in diagnosis because there is no selective decline of putaminal activity in the healthy people.

The second limitation is that we did not suggest correlative data of the severity of PD or comparison data according to the severity of PD. Actually, there was no significant correlation between the Hoehn and Yahr grade and uptake value or change in uptake values during dual

point imaging in this study. This might be due to the small sample size. An increase in the number of patients might have resulted in a more significant outcome. Although the primary end point of the present study is to select the appropriate imaging time using F-18 FP-CIT dual point PET/CT imaging for the diagnosis of PD, one can expect a significant correlation between the severity of PD between the uptake value or change in uptake values in a future larger study.

Conclusions

The results of this study indicate that delayed F-18 FP-CIT imaging has no added benefit in the diagnosis of Parkinson's disease. Therefore, the 90-min image alone is sufficient for diagnosing PD.

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Conflict of interest None.

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