Evaluation of Early-Stage Parkinson’s Disease with 99mTc-TRODAT-1 Imaging

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Parkinson’s disease is a progressive neurodegenerative disorder characterized by a selective loss of dopamine in the striatum. Problems remain in the accurate diagnosis of Parkinson’s disease. A 99mTc-labeled tropane derivative that binds to dopamine transporter with high selectivity is [2-[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methy]l][2-mercaptopethyl]amino[ethyl][amino]ethanethiolato(3-)N2,N2',S2,S2']oxo-[1R-(exo-exo)] (TRODAT-1). The purpose of this study was to investigate the potential usefulness of 99mTc-TRODAT-1 imaging in the evaluation of patients with early-stage Parkinson’s disease. Methods: Thirty-four patients with early-stage idiopathic Parkinson’s disease were recruited. For all patients, the Parkinson’s disease was stage 2 or less as assessed by the Hoehn and Yahr scale. Seventeen age-matched healthy volunteers (8 men, 9 women) served as controls. 99mTc-TRODAT-1 was prepared from a lyophilized kit. Brain SPECT imaging was performed between 165 and 195 min after injection, using a double-head camera equipped with fanbeam collimators. Specific uptake in the striatum and its subregions, including the putamen and caudate nucleus, was calculated and compared with that of the other sides and of healthy volunteers. Results: A continuous reduction in specific striatal uptake of 99mTc-TRODAT-1 with increasing disease severity was found in Parkinson’s disease patients (control vs. stage I vs. stage II, 1.98 vs. 1.62 vs. 1.22, respectively, P < 0.01). The changes were magnified by measurement of specific putaminal uptake (control vs. stage I vs. stage II, 1.81 vs. 1.27 vs. 0.94, respectively, P < 0.01). The mean values of specific putaminal uptake contralateral to the more affected limbs were significantly decreased compared with the ipsilateral sides in both stage I and stage II groups (1.02 vs. 1.49 for stage I and 0.73 vs. 1.14 for stage II, P < 0.01). Moreover, a significant loss of putaminal uptake ipsilateral to the symptoms was found in the stage I group compared with the healthy volunteers (1.49 vs. 1.81, P < 0.01). The difference became greater when the posterior putaminal uptakes were compared. No remarkable adverse reactions were found in either healthy volunteers or Parkinson’s disease patients during or after imaging. Conclusion: For clinical practice, 99mTc-TRODAT-1 may serve as a useful imaging agent for the early detection of Parkinson’s disease.

Key Words: 99mTc-TRODAT-1; dopamine transporter; SPECT; Parkinson’s disease


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Patients had taken antiparkinsonian medication (L-dopa) for various healthy volunteers. Seven patients were drug naive. The other more affected limbs was compared with that of the other side and striatum, putamen, and caudate nucleus was measured bilaterally. The mean age of the subjects was 67 years (range, 54–79 y; mean age, 67 ± 6 y). Specific uptake in the stage I group compared with the healthy volunteers and on the ipsilateral side in patients with stage I Parkinson’s disease was also analyzed (26).

### MATERIALS AND METHODS

#### Subjects

Thirty-four patients with early-stage Parkinson’s disease were studied. Parkinson’s disease was diagnosed according to generally accepted criteria (24). The severity of Parkinson’s disease was assessed using the Hoehn and Yahr scale (HYS) (25). In addition, the patients we selected were >40 y old and response was to a single-dose levodopa challenge. Fifteen patients were in HYS stage I (7 men, 8 women; age range, 47–78 y; mean age ± SD, 62 ± 9 y), and 19 were in HYS stage II (10 men, 9 women; age range, 54–79 y; mean age, 67 ± 8 y). Specific uptake in the striatum, putamen, and caudate nucleus was measured bilaterally. The mean activity of the more affected side (contralateral to the more affected limbs) was compared with that of the other side and of healthy volunteers. Seven patients were drug naive. The other patients had taken antiparkinsonian medication (L-dopa) for various periods but had discontinued it at least 24 h before and until completion of the studies.

Seventeen age-matched healthy volunteers (8 men, 9 women; age range, 45–76 y; mean age, 63 ± 9 y) served as controls. On the basis of a screening interview, none of the healthy volunteers had a history of neuropsychiatric disorders or a family history of movement disorders. For at least 3 mo, none had taken medication known to affect brain function.

All patients and healthy volunteers gave written informed consent. The study was approved by the ethical committees of our hospital and the Department of Health of the Republic of China.

#### Radiopharmaceuticals

99mTc-TRODAT-1 was prepared as has been reported (11), with minor modifications. Briefly, it was prepared from a lyophilized kit by adding 1.110 MBq freshly eluted 99mTc-pertechnetate to 5 mL saline preparation (17). The 99mTc-TRODAT-1 was obtained in a neutral solution (pH, 7.0–7.5) with >90% radiochemical purity over 6 h as determined by high-performance liquid chromatography. The shelf life of the lyophilized kit was >2 mo when it was stored at room temperature.

#### Imaging and Data Acquisition

All subjects consumed a low-protein diet for 24 h before the 99mTc-TRODAT-1 examinations. The subjects were placed supine, with their head fixed in a holder. After a single bolus injection of 740 MBq 99mTc-TRODAT-1, 15 dynamic images of the brain were acquired during 30 min (2 min per frame). The brain SPECT images were then acquired between 165 and 195 min after injection using a double-head camera equipped with fanbeam collimators (Helix SPX; Elscint, Haifa, Israel). Data were acquired in a 128 × 128 matrix with a 1.4 zoom through 360° (180° for each head) rotation at 3 intervals, for 30 s per angle step. Images were reconstructed using backprojection with a Metz filter. Attenuation correction was performed by the first-order method of Chang. The SPECT images were analyzed along the level of the canthomeatal line. Regions of interest were marked for one side of the striatum in reference to the corresponding MR image and were fitted to the other side. Regions of interest were drawn over the whole striatum, putamen, and caudate nucleus of each hemisphere on composite images of the 3 slices with the highest basal ganglia activity. The occipital cortices (OC) were also drawn in the same way and served as background areas. The specific uptake was calculated by subtracting the mean counts per pixel in the OC from the mean counts per pixel in the whole striatum, putamen, or caudate nucleus and dividing the result by the mean counts per pixel in the background, that is, (striatum – OC)/OC, (putamen – OC)/OC, or (caudate nucleus – OC)/OC. The posterior putaminal uptake in healthy volunteers and on the ipsilateral side in patients with stage I Parkinson’s disease was also analyzed (26).

#### Statistics

Multiple ANOVA for multigroup comparisons was performed using SPSS 9.0 software (SPSS Inc., Chicago, IL) for Windows (Microsoft, Redmond, WA). If the result was significant, the Dunnett multicomparsion test was used to compare the normal mean value with the values of the other groups. The Student t test for paired samples was performed for within-group comparison of outcome measures between ipsilateral and contralateral sides and between those of the healthy volunteers. Significance was defined as P < 0.05. Results are reported as the mean ± SD.

### RESULTS

The images were interpreted both visually and by semi-quantitative analysis. In the dynamic studies, we found that radioactivity accumulated in the basal ganglia area of each subject. On SPECT images, a better contrast of radioactivity between the striatum and adjacent brain tissue was observed in healthy volunteers than in patients (Fig. 1).

Significant differences in specific striatal uptake were found among healthy volunteers, patients with stage I disease, and patients with stage II disease (1.98 ± 0.24, 1.62 ± 0.11, and 1.22 ± 0.12, respectively, P < 0.01), as shown in Table 1 and Figure 2. Greater loss of uptake occurred in the putamen than in the caudate nucleus and contralateral to the more affected limbs, although striatal uptake was bilaterally reduced. The specific putaminal uptake decreased markedly in Parkinson’s disease patients (control vs. stage I vs. stage II, 1.81 ± 0.18 vs. 1.27 ± 0.14 vs. 0.94 ± 0.20, P < 0.01) (Table 1; Fig. 3). The average decrease in putaminal uptake contralateral and ipsilateral to symptoms or more affected limbs was 44% and 18%, respectively, in stage I and 60% and 37%, respectively, in stage II (Table 1; Figs. 4 and 5). Although overlap still existed in 8 cases, a significant loss of putaminal uptake ipsilateral to the symptoms was found in the stage I group compared with the healthy volunteers.
(1.49 ± 0.22 vs. 1.81 ± 0.18, \( P < 0.01 \)). The difference became greater when the posterior putaminal uptakes were compared (1.29 ± 0.17 vs. 1.67 ± 0.15), and in only 4 cases was there overlap (Fig. 6).

No significant change in mean uptake by the caudate nucleus—either in its entirety or for each side considered separately—was observed between stage I patients and healthy volunteers, but a significant decrease was seen in stage II patients (2.13 ± 0.31 vs. 1.51 ± 0.17, \( P < 0.01 \)) (Table 1). No remarkable adverse reactions were found in either healthy volunteers or Parkinson’s disease patients during or after imaging.

DISCUSSION

In patients with early-stage Parkinson’s disease, a significant loss of striatal uptake of \( ^{99m} \text{Tc-TRODAT-1} \) at 165–195 min after injection was found using conventional double-head nuclear medicine facilities. The profound differences in specific uptake in the striatum and especially in the putamen in early-stage Parkinson’s disease enabled us to evaluate patients by visual inspection of images. The significant reduction of putaminal uptake ipsilateral to the symptoms, especially posteriorly, in stage I patients may provide a clue for following disease progression. Our results support previous observations using either SPECT \((8,14,27,28)\) or PET \((21,29)\) and suggest that \( ^{99m} \text{Tc-TRODAT-1} \) may be a useful agent for DAT imaging to assess early dopaminergic neuron loss. In addition, \( ^{99m} \text{Tc-TRODAT-1} \) DAT imaging appears to be safe for humans \((30)\).

The diagnosis of Parkinson’s disease still relies mainly on observation of typical clinical symptoms and signs. Notably, the accuracy of the clinical diagnosis of Parkinson’s disease is approximately only 70%–80% on the basis of clinicopathologic studies \((1)\). It is therefore crucial to find a clinically feasible way to more easily evaluate the etiology and severity of the disease. Prior studies have shown that PET can determine the integrity of the dopaminergic neurons in vivo and thus play an important role in the early diagnosis and differentiation of so-called parkinsonian syndromes \((4,31,32)\). In addition, many promising studies using SPECT imaging with \( ^{123} \text{I} \)-labeled tracers have been reported. Because \( ^{123} \text{I} \) is produced in a cyclotron, its high cost and lack of availability in most nuclear medicine departments limit its routine clinical use. Kit-based \( ^{99m} \text{Tc} \)-labeled radiopharmaceuticals combined with conventional diagnostic cameras provide an ideal means for routine use. In this study, we used a double-head camera equipped with a fanbeam collimator, both of which are commonly available.

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy volunteers</th>
<th>Stage I Parkinson’s disease</th>
<th>Stage II Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>1.98 ± 0.24</td>
<td>1.62 ± 0.11(^*)</td>
<td>1.22 ± 0.12(^*)</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.81 ± 0.18</td>
<td>1.27 ± 0.14(^*)</td>
<td>0.94 ± 0.20(^*)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>1.02 ± 0.20</td>
<td>0.73 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>1.49 ± 0.22(^*)</td>
<td>1.14 ± 0.29(^*)</td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.13 ± 0.31</td>
<td>1.97 ± 0.21(^*)</td>
<td>1.51 ± 0.17(^*)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>1.95 ± 0.22</td>
<td>1.45 ± 0.24</td>
<td></td>
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<tr>
<td>Ipsilateral</td>
<td>1.99 ± 0.34</td>
<td>1.58 ± 0.23(^*)</td>
<td></td>
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</tbody>
</table>

\(^{*}\) \( P < 0.01 \) compared with volunteers or adjacent group.
\(^{†}\) \( P < 0.01 \) compared with volunteers or contralateral side.
\(^{‡}\) \( P < 0.01 \) compared with volunteers only.

Data are expressed as mean ± SD. Contralateral means side opposite to symptoms or more affected limbs. Ipsilateral means side of symptoms or more affected limbs.

FIGURE 1. \( ^{99m} \text{Tc-TRODAT-1} \) SPECT in transverse views of healthy volunteer (A) and of patients with HYS stage I (B) and stage II (C) Parkinson’s disease. Asymmetric striatal uptake was observed, with more profound loss contralateral to symptoms or more affected limbs.

FIGURE 2. Specific striatal uptake of \( ^{99m} \text{Tc-TRODAT-1} \) in healthy volunteers and in patients with HYS stage I and stage II Parkinson’s disease.
Progress in neuroscience has made evident that nigral dopaminergic projections to the striatum, especially those to the putamen, are targeted in Parkinson’s disease, whereas those to the caudate nucleus are relatively spared (5,7,10). Our results agree with previous SPECT and PET studies that showed a correlation between DAT density and disease severity (8,16,29). On the other hand, pathologic evidence has disclosed a more severe depletion of dopamine in the putamen than in the caudate nucleus in Parkinson’s disease patients (4,5,8,27), in contrast to many Parkinson’s disease-like disorders, which usually show a more uniform and symmetric striatal loss of dopaminergic activity (4,10,33). These histopathologic differences provide an assessable approach for the early diagnosis of Parkinson’s disease and perhaps can be used to discriminate etiologies of parkinsonism by measuring specific putaminal uptake, especially in the posterior portion (8,15,27,34). In this study, we found an obvious loss of putaminal uptake contralateral to the more affected limbs. The specific putaminal uptake contralateral to symptoms in the stage 1 group was also significantly reduced compared with the ipsilateral side and the healthy volunteers. These results agree with recent studies showing that binding of $^{99m}$Tc-TRODAT-1 to DAT is sensitive to minimal changes in the availability of DAT (15,16,20). The greater decrease of $^{99m}$Tc-TRODAT-1 uptake in putamen than in caudate nucleus may enhance the sensitivity of $^{99m}$Tc-TRODAT-1 imaging for early detection of Parkinson’s disease (15,16).

Interestingly, compared with the healthy volunteers, patients in the stage I group also had a significantly decreased uptake in putamen ipsilateral to the symptomatic side. This difference became more pronounced when the comparison focused on the posterior putamen, suggesting that mea-
significantly differ among the groups. Although we discon-

99m Tc-TRODAT-1 imaging may not be limited to disease diagno-

The decline of DAT density was found to be independent of sex (37). However, the effect of age on DAT density in humans is still controversial. Muller et al. (37) found no significant effect of age on relative or absolute striatal uptake in their Parkinson’s disease patients. Others, how-

development of DAT binding in patients with mild Parkinson’s
disease may permit earlier or even presymptomatic identi-

CONCLUSION

The findings of this study indicate that 99m Tc-TRODAT-1 is a clinically feasible radiopharmaceutical for studying DAT in patients with Parkinson’s disease. The high target-to-noise ratio for 99mTc-TRODAT-1 and significant reduc-

REFERENCES

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