Evaluation of Therapeutic Response to Donepezil by Positron Emission Tomography

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Abstract

Background

Donepezil hydrochloride (Donepezil) is an acetylcholinesterase inhibitor (AChEI) that is used for the symptomatic treatment of Dementia of the Alzheimer's Type (DAT). Recently, the effects of AChEI in patients with DAT have been investigated using positron emission tomography (PET) or single photon emission computed tomography (SPECT). This study is to evaluate the usefulness of fluorine-18-fluorodeoxyglucose (FDG)-PET in assessing the therapeutic response of Donepezil to DAT using Regions of Interest (ROI) analysis.

Methods

The participants included eleven outpatients diagnosed as having DAT according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The patients were performed FDG-PET before initiating Donepezil therapy and after 12 weeks of medication. Cognitive change was measured using the Japanese version of the Alzheimer's disease Assessment Scale cognitive subscale (ADAS-J cog) and the group was divided into Responders and Non-responders based on these results. We used FDG-PET to investigate glucose metabolism of the brain and measured FDG uptake in the ROI set in each lobe of the brain. Then the ratios of the post-treatment uptake to pre-treatment uptake were determined.

Results

In the Responders, the mean ratios in the frontal, temporal, occipital, parietal, and temporoparietal lobes were 2.18, 1.62, 1.15, 1.12, and 1.09 respectively. The mean ratios of the Non-responders were 0.69, 0.88, 0.75, 0.98, and 0.68 respectively. Significant differences were found between the ratios of the Responders and Non-responders in the frontal and occipital lobes (p<0.05).

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Conclusions
These findings suggest that FDG-PET could be useful for the evaluation for monitoring response to Donepezil.

Key Words: Donepezil; FDG-PET; Alzheimer; ADAS-J cog; ROI analysis

Introduction
Donepezil hydrochloride (Donepezil) is a highly centrally selective inhibitor of acetylcholinesterase (AChE) which is used for the symptomatic treatment of Dementia of the Alzheimer's Type (DAT). Acetylcholinesterase inhibitors (AChEIs) have an effect that delays the progression of cognitive dysfunction in DAT and occasionally improves cognitive function\(^1\text{-}^5\). Although cognitive improvement occurs in 12% to 60% of the patients across the agents\(^1\text{-}^6\), AChEIs have not been effective for some patients with DAT regardless of disease stage\(^1\text{-}^3\text{-}^5\). Furthermore, it is not easy to evaluate the therapeutic response of Donepezil to patients with DAT for various reasons such as clinical symptoms or progression of the disease. Therefore, an index for a more objective evaluation of the therapeutic effect of AChEIs on patients with DAT is needed.

It has been established that regional metabolic rates for glucose assessed by fluorine-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with DAT provides a sensitive, in vivo metabolic index of DAT\(^7\). Many studies have reported that reduced cerebral blood flow (CBF) and metabolism are observed firstly in the temporoparietal brain regions and the posterior cingulate cortex of patients with DAT. Recently, the effect of AChEIs in patients with DAT have been reported using PET or single photon emission computed tomography (SPECT)\(^4\text{-}^8\text{-}13\).

We examined the usefulness of FDG-PET in assessing the therapeutic response to Donepezil in patients with DAT using Regions of Interest (ROI) analysis.

Methods
The subjects of this study were eleven right-handed outpatients (3 men, 8 women; age range, 61-84 y; mean age, 72.1 y) diagnosed as having DAT by the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)\(^14\) (Table 1). The inclusion criterion of this study was a dementia severity below grade 2 on the Clinical Dementia Rating (CDR) scale. In order to evaluate cognitive function, the Revised Hasegawa Dementia Scale (HDS-R: score 0-30, with 0 being the most severe)\(^15\) was used to all subjects with DAT. The HDS-R has been used exclusively in East Asian countries as a screening test for DAT. The optimal cut-off scores of the HDS-R for mild DAT are 20/21 in Japan. We assessed cognitive change using the Japanese version of the Alzheimer's disease Assessment Scale cognitive subscale (ADAS-J cog)\(^16\). This reliable and valid neuropsychological test of cognition has 11 items which test a variety of domains, including spoken language ability, comprehension of spoken language, recall of test instructions, word-finding difficulty, following commands, naming, orientation, ideational and constructional praxis, word recall, and word recognition. This test can be administered in approximately 40 minutes. Maximal impairment on the ADAS-J cog is indicated by a score of 70, with lower scores indicating less severity. We defined patients
Table 1. DSM-IV Diagnostic criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

whose total score on ADAS-J cog changed by more than −1 point as Non-responders and those under −1 point as Responders. None of the participants in this study had diabetes mellitus. Each patient had undergone brain perfusion SPECT with Tc 99m-ethyl cysteinate dimmer before this study. To confirm the diagnosis of DAT, each SPECT image was analyzed using the easy Z-score imaging system (eZIS)\textsuperscript{17}. The Institutional Review Board of Osaka City University Hospital approved this study protocol, and informed consent was obtained from each patient and his or her family representative after a detailed explanation of the study.

All patients had fasted for at least 4 hours before PET scanning. Each patient underwent the first PET scan before the first dose of Donepezil. After the first PET examination, patients received 3 mg/day of Donepezil for the first 2 weeks, and then received 5 mg/day thereafter if tolerated. A second PET scan was completed after 12 weeks of Donepezil therapy. FDG was produced with the NKK-Oxford superconducting cyclotron and NKK synthesis system. A HEADTOME N SET-1400W-10 (Shimadzu Corp., Japan), which has 4 detector rings providing 7 contiguous slices at 13 mm intervals, was employed for PET studies. The effective spatial resolution was 14 mm in Full Width Half Maximum. Before emission scanning, transmission scans were performed with a $^{68}$Ge/$^{186}$Ga ring source for attenuation correction. Images were obtained from 40 to 55 minutes after intravenous injection of 185-370 MBq FDG after a 4-hour fast.

Five regions of interests (ROIs: circles 3 pixels in diameter) were placed on each area of FDG uptake within the left and right frontal, temporal, temporoparietal, parietal, occipital lobes, and cerebellar hemisphere. FDG uptake in ROIs on each lobe was measured, then divided by the mean count in the cerebellum normalized by the mean count per pixel in each ROI. These regions are shown in Figure 1. To evaluate the therapeutic effect of Donepezil, we calculated the ratio of the mean count after treatment to the count before treatment.
Figure 1. Five pairs of regions of interest (ROIs: circles 3 pixels in diameter) placed on the left and right frontal (a), temporal (b), parietal (c), temporoparietal (d), and occipital (e) lobes. Cerebellar reference regions were defined on the bilateral cerebellum (f).

Statistical analysis was performed with SPSS for Windows 16.0 (SPSS Japan, Tokyo, Japan). Categorical variables, such as gender, were compared with chi-square and Fisher-exact tests. We used the Mann-Whitney U-test to compare clinical characteristics and the ratio of the mean count after treatment to the count before treatment between Responders and Non-responders. All statistical tests were two-tailed and reported at p<0.05.

Results

Table 2 shows the demographic and clinical characteristics of Responders and Non-responders divided according to the changes of total scores of ADAS-J cog. Of the 11 patients, 7 were Responders and 4 were the Non-responders. There were no significant differences between Responders and Non-responders with respect to patient age, age at disease onset, duration of DAT/dementia, years of education, HDS-R score or total score on ADAS-J cog before treatment. In addition, chi-square analysis did not show any significant difference between the groups with regard to gender distribution or family history of dementia. The average change in the total score on ADAS-J cog in the Responders was -6.27, while in Non-responders, it was 4.25. All
Table 2. Demographic and clinical characteristics of Responders and Non-responders

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=7)</th>
<th>Non-responders (n=4)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.7 (8.2)</td>
<td>74.5 (3.8)</td>
<td>0.296</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>85.7</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Onset, years</td>
<td>69.7 (8.4)</td>
<td>73.8 (4.0)</td>
<td>0.257</td>
</tr>
<tr>
<td>Family history of dementia (%)</td>
<td>42.9</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Duration of dementia, years</td>
<td>1.2 (0.8)</td>
<td>0.9 (0.7)</td>
<td>0.392</td>
</tr>
<tr>
<td>Education, years</td>
<td>9.0 (3.3)</td>
<td>8.8 (1.5)</td>
<td>0.360</td>
</tr>
<tr>
<td>HDS-R</td>
<td>19.6 (6.0)</td>
<td>15.8 (3.5)</td>
<td>0.256</td>
</tr>
<tr>
<td>ADAS-J cog pre</td>
<td>18.7 (8.1)</td>
<td>17.3 (11.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>ADAS-J cog post</td>
<td>12.5 (7.4)</td>
<td>21.6 (11.4)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

HDS-R, the Revised Hasegawa Dementia Scale; and ADAS-J cog, the Japanese version of the Alzheimer’s disease Assessment Scale cognitive subscale.

Table 3. The total scores of ADAS-J cog and the ratios of uptake in each lobe to that in the cerebellum in each patient

<table>
<thead>
<tr>
<th>gender</th>
<th>age</th>
<th>HDS-R</th>
<th>ADAS-J cog total score</th>
<th>the ratios of each lobe to the cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>before</td>
<td>after</td>
</tr>
<tr>
<td>Responders</td>
<td></td>
<td></td>
<td>frontal</td>
<td>temporal</td>
</tr>
<tr>
<td>case1</td>
<td>male</td>
<td>66</td>
<td>19</td>
<td>13.7</td>
</tr>
<tr>
<td>case2</td>
<td>female</td>
<td>70</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>case3</td>
<td>female</td>
<td>63</td>
<td>26</td>
<td>12.7</td>
</tr>
<tr>
<td>case4</td>
<td>female</td>
<td>61</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>case5</td>
<td>female</td>
<td>76</td>
<td>24</td>
<td>14.7</td>
</tr>
<tr>
<td>case6</td>
<td>female</td>
<td>75</td>
<td>13</td>
<td>29.7</td>
</tr>
<tr>
<td>case7</td>
<td>female</td>
<td>84</td>
<td>10</td>
<td>30.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the average of the ratio (SD)</td>
<td>2.18 (1.58)</td>
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<tr>
<td>Non-responders</td>
<td></td>
<td></td>
<td>before</td>
<td>after</td>
</tr>
<tr>
<td>case8</td>
<td>male</td>
<td>69</td>
<td>14</td>
<td>33.3</td>
</tr>
<tr>
<td>case9</td>
<td>female</td>
<td>77</td>
<td>17</td>
<td>15.6</td>
</tr>
<tr>
<td>case10</td>
<td>female</td>
<td>77</td>
<td>12</td>
<td>6.9</td>
</tr>
<tr>
<td>case11</td>
<td>male</td>
<td>75</td>
<td>20</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the average of the ratio (SD)</td>
<td>0.69 (0.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p</td>
<td>0.023**</td>
</tr>
</tbody>
</table>

HDS-R, the Revised Hasegawa Dementia Scale; and ADAS-J cog, the Japanese version of the Alzheimer’s disease Assessment Scale cognitive subscale. *1, the average of the ratio of the mean count after treatment to the count before treatment; and *2, p<0.05.

patients showed typical pattern for Alzheimer’s disease on PET images and significant regional CBF reduction in the posterior cingulate gyrus and/or precuneus region on SPECT images using eZIS.

The ratios of the mean post-treatment uptake to the pre-treatment uptake in five bilateral pairs of ROIs on portions of each lobe are shown in Figure 2. Table 3 shows the total scores of ADAS-J cog and the ratios of uptake in each lobe to that in the cerebellum in each patient. In Responders, the averages of the ratios of the mean counts after treatment to the counts pre-
treatment in the frontal, temporal, occipital, parietal, and temporoparietal lobes were 2.18, 1.62, 1.15, 1.12, and 1.09 respectively, while those in the Non-responders were 0.69, 0.88, 0.75, 0.98, and 0.68 respectively (Table 3). In the frontal and occipital lobes, the Responders showed significantly increased glucose metabolism compared with that in Non-responders \( p<0.05 \) (Fig. 2).

**Figure 2.** The ratios of the mean post-treatment uptake to the pre-treatment uptake in five bilateral pairs of ROIs on portions of each lobe. \(*^1\); the ratio of the mean count after treatment to the count before treatment; and \(*^2\); \( p<0.05 \).

**Discussion**

We attempted to evaluate the therapeutic response to Donepezil in patients with DAT using FDG-PET in this study. After treatment, Responders showed increased FDG uptake in the frontal, temporal, and occipital lobes on average. Non-responders showed decreased uptake in the frontal, temporal, occipital, and temporoparietal lobes. These findings suggest that the therapeutic response to Donepezil could be evaluated by measuring glucose metabolism in brain regions using FDG-PET.

Short-term treatment with different AChEIs such as Tacrine, Donepezil, Physostigmine, Metrifonate, Rivastigmine, and Galantamine have shown an increase in CBF or glucose metabolism in patients with DAT\(^{4,5,11,18,20}\). Especially, frontal metabolism or CBF increase during AChEIs treatment has often been reported\(^{4,5,11}\). In this study, we also found a marked increase in glucose metabolism especially in the frontal lobes of Responders. This finding is consistent with the findings of previous PET studies regarding AChEIs treatment. Tune et al also evaluated the effects of 24 weeks Donepezil treatment on regional glucose metabolism in the patients with DAT by using ROI analysis\(^{23}\). They reported that significant treatment differences for the mean percentage change from baseline in regional brain glucose metabolism were observed in the right parietal lobe and left temporal lobe in addition to bilateral frontal lobe. These results may have varied with differences in the duration of the treatment, the dose or the use of different reference
region in the ROI method. We evaluated the therapeutic response at 12 weeks because the Japanese clinical research on Donepezil therapy revealed that significant differences were found after 12 weeks of the treatment between Donepezil and placebo groups\(^{16}\). However, some studies on AChEIs suggested the difference became statistically significant after 24 weeks treatment\(^{2,3,13}\). Therefore we also have to make further investigation about 24 weeks treatment to clarify the effect of the Donepezil therapy.

At present, a cognitive performance test such as the Alzheimer's disease Assessment Scale cognitive subscale\(^{16,19,21}\) or the Mini-Mental State Examination is used to monitor the response to AChEIs\(^{4,22}\). However, the result of these tests may be influenced by the subjective judgment of the examiner and the mental condition of the patient, such as depressive mood, hallucination or delusion. Therefore, we designed this study to find a method that would facilitate evaluation of therapeutic response in patients with DAT regardless of clinical symptoms.

Functional neuroimaging methods (such as SPECT or PET) are widely used in the early diagnosis of DAT because reduced CBF and metabolism in patients with DAT is typically observed in the temporoparietal brain region and posterior cingulate cortex\(^{8}\). DAT patients can undergo PET in a resting state without mental task and the data are not influenced by the patient’s transient level of motivation or physical condition. Particularly, FDG-PET provides more quantitative and sensitive data, so it is considered suitable for evaluation of therapeutic response. Therefore, we use FDG-PET to evaluate the therapeutic response to Donepezil in patients with DAT in this study.

Recently, most neuroimaging studies have investigated therapeutic responses to AChEIs using voxel-by-voxel analysis\(^{4,5,11,19,20}\). We reported the usefulness of SPECT to evaluate treatment response to Donepezil in patients with DAT by three-dimensional stereotaxic ROI template\(^{19}\). In these analyses spatial normalization of brain images to a standard stereotactic space is performed in order to facilitate the anatomical accuracy of subsequent voxel-based analysis\(^{5}\). However, it has been pointed out that brain atrophy cannot be completely standardized on these analyses. Therefore, we used ROI analysis in this study in order to minimize the influence of variations in brain atrophy among patients.

The reason for increased glucose metabolism in the Responders remains unclear. FDG-PET can reflect functional activity\(^{23}\), but can not detect sensitive changes in the cholinergic nervous system\(^{24}\). Shinotoh, et al\(^{9}\) reported that Donepezil reduced AChE activity in the cerebral cortex using PET and N-(\(^{13}\)C) methylpiperidin-4-yl acetate and suggested that the effect was likely caused by improved cholinergic activity due to inhibition of AChE in the brain. The contribution of the cholinergic deficit to cognitive abnormalities is further supported by correlations between the severity of acetylcholine deficiency and the degree of cognitive impairment in DAT\(^{25}\). These findings suggested that FDG-PET indirectly shows changes in functional activity caused by improvement in cholinergic activity after Donepezil treatment.

There are some limitations to this study. First, the sample size in this study is too small and may not reflect a typical DAT population. Second, there is a problem in the method of semiquantifying regional glucose metabolism values in this ROI analysis study. In most PET studies of DAT, cerebellar metabolism has been used as a reference region because it is less involved in the progression of DAT\(^{26-28}\). However, there is a report that cerebellar glucose metabolism is significantly reduced in advanced DAT\(^{29}\). Therefore, we excluded cases over
CDR=2 to minimize this effect and we will examine this issue further using the primary visual region as a reference region, since that area is much less involved in the disease. Third is the general limitation of ROI placement. This method has problems including inadequate reproducibility of the ROI designation procedure and inadequate objectivity\textsuperscript{19}. Fourth, we are not able to exclude the effect of stress response during the PET scan procedure. The brain metabolism in some patients might have at least partly reflected this effect rather than the effect to Donepezil treatment. Fifth, there is a problem in the way to define the therapeutic response. The definition of the response in a progressive neurodegenerative disease can be challenging. Studies designed to evaluate definition of treatment response in patients with DAT are scarce\textsuperscript{6}. Although there were few evidences, we regarded patients who changed by more than –1 point as Responders on ADAS-J cog in this study, because even placebo patients showed some improvement within several weeks and the mean change scores of placebo groups in ADAS-J cog was about –1 point at 12 weeks\textsuperscript{16}. We need further research to verify this definition. Further studies will be needed to investigate the effect of Donepezil on glucose metabolism in the brains of patients with DAT. Despite these limitations, the present findings suggest that FDG-PET could be useful for monitoring the response to Donepezil in patients with DAT.

Acknowledgements

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References

Evaluation of Donepezil Treatment by PET


