Fundamental studies on radiotracers intended for receptor imaging in dementia
Knol, R.J.J.

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CHAPTER 9

DECREASED CORTICAL MUSCARINIC RECEPTOR DENSITY IN PDD VS PD PATIENTS AS ASSESSED BY IN-VIVO [123I]IODODEXETIMIDE SPECT

Remco J.J. Knol a,b, J.L.W. Bosboom c, E.Ch. Wolters d, Kora de Bruin d, J. Habraken d, B.L.F. van Eck-Smit a, Jan Booij a,b

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a Department of Nuclear Medicine, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands. b Graduate School of Neurosciences, Amsterdam, The Netherlands. c Department of Neurology, VU Medical Center, Amsterdam, The Netherlands

Abstract

Cognitive impairment in Parkinson’s disease (PD) and Parkinson’s disease related dementia (PDD) are associated with deficiencies in the cholinergic neurotransmitter system. Moderate improvements on cognition due to acetylcholinesterase inhibitors (AChEIs) have been reported in a subgroup of PDD patients. SPECT imaging of the cholinergic neurotransmitter system, for instance using the muscarinic receptor radiotracer [123I]iododextetimide, may help to select patients that could benefit from AChEIs and may be useful to monitor disease progression. The aim of the present study was to investigate the differences in muscarinic receptor availability in the brain of PDD versus PD patients, as measured by in-vivo [123I]iododextetimide SPECT.

[123I]iododextetimide SPECT was performed in 13 subjects (6 PD, 7 PDD). The obtained images were fitted to a standard brain template, normalized to non-specific tracer uptake in white matter and analyzed using statistical parametric mapping (SPM99).

No increases in tracer binding were detected in the brain of PDD versus PD patients. However, significant decreases in tracer binding (puncorrected <0.005) in the PDD group as compared to the PD group were detected in both the left and right temporal cortex, left hippocampus, and the posterior cingulate cortex.

In conclusion, the present study demonstrates decreased muscarinic receptor binding by [123I]iododextetimide in PDD versus PD in brain areas that are involved in memory function. The findings suggest that reduced muscarinic receptor binding in these brain areas could be used as a marker PDD and might be of value for the selection of PDD patients that are likely to respond to AChEIs.
Introduction
Parkinson’s disease (PD) and Parkinson’s disease related dementia (PDD) are characterized primarily by dopaminergic degeneration, but are also associated with deficiencies in the cholinergic neurotransmitter system. In up to 60% of PD patients, cognitive deficits that frequently accompany this disease, progress to PDD. In PDD, cognitive impairment correlates with disturbances of cortical cholinergic activity, which arise from degeneration of the nucleus basalis of Meynert (NBM). Moderate improvements on cognition due to acetylcholinesterase inhibitors (AChEIs) have been reported in PDD. Importantly, not all of these patients respond equally well on AChEIs. SPECT or PET imaging of the cholinergic neurotransmitter system may help to select patients that could benefit from AChEIs and may be useful to monitor disease progression. The muscarinic receptor radiotracer [123I]Iododexetimide has been evaluated previously for imaging of the muscarinic system in Alzheimer’s dementia.

In this study, we investigated the differences in muscarinic receptor availability in the brain of PDD versus PD patients, by means of [123I]Iododexetimide SPECT, the hypothesis being that a decrease in muscarinic receptor availability would be present in cortical areas of PDD patients due to the degenerative changes in the NMB.

Materials and Methods
Subjects
A total of 13 patients, diagnosed clinically according to the clinical diagnostic criteria of the UK Parkinson’s Disease Society Brain Bank, were recruited from the outpatient clinic of movement disorders. PD was staged according to the Hoehn and Yahr scale (H&Y; range 0-5 with higher scores indicating more advanced disease stage). PDD patients additionally fulfilled DSM-IV-criteria (American Psychiatric Association, 1994) for dementia and had a Mini Mental State Examination (MMSE) score of 24 or lower out of a maximum of 30 points, with lower scores indicating worse cognition. PD patients did not experience difficulties with cognitive functioning in daily life and on clinical examination, did not display any signs of dementia. The study population included six PD patients (one woman and five men; mean age 65yr; range 53-76yr) and seven PDD patients (three women and four men; mean age 74yr; range 64-82yr). Exclusion criteria included a diagnosis of other neurodegenerative disease, severe depression or psychotic symptoms, alcohol or drug abuse, cholinergic drugs or the use of neuroleptics.
All subjects gave informed written consent and the study was approved by the local medical ethical committee.

**Image acquisition and analysis**

Thyroid gland uptake of free radioactive iodine was prevented by administration of potassium iodide. \([^{123}\text{I}]\)Iododextimide (specific activity 185MBq/nmol; radiochemical purity 98.0%) was a generous gift from GE Healthcare, Eindhoven, The Netherlands. The radiosynthesis of this radiotracer was described earlier\(^6\).

All subjects received approximately 185MBq \([^{123}\text{I}]\)Iododextimide intravenously, 8 hours before the SPECT acquisition\(^5\). Images were acquired using a brain-dedicated SPECT camera (Strichman Medical Equipment inc, Medfield, Mass, USA), equipped with 12 individual crystals with focusing collimators. The energy window was set at 135-190keV and 5mm slices were acquired during 150 sec as a 64x64 matrix parallel to the orbitomeatal line. Image reconstruction and Gaussian smoothing was performed by the Neurofocus software (NeuroPhysics Corporation, Shirley, USA). After software based matching of the scans to the T1 Montreal Neurological Institute (MNI) template and after conversion to Analyze format, images were imported in Matlab 6 (MathWorks, Inc.). Radioactive uptake within a white matter VOI-template was considered non-specific uptake and used to normalize each SPECT data set. Then voxel-by-voxel analysis was performed by statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London).

**Statistical Analysis**

Differences were analyzed by SPSS 15.0 using a student T-test for age, disease duration and MMSE-scores, whereas H&Y-scores were analyzed using a Mann-Whitney U test. P-values <0.05 were considered significant. Between-group analysis of the SPM data was performed by Matlab 6 and SPM99 using a 2-sample T-test with correction for multiple comparisons, using an extend threshold of k=50 voxels and \(p_{uncorrected} <0.005 (T=3.11)\) were considered significant.

**Results**

The characteristics of participants are summarized in Table 9.1. The age of the PD group was not significantly different from the PDD group (\(P=0.110\)). MMSE scores were significantly lower in the PDD group.
Table 9.1. Study group characteristics. Abbreviations: H&Y score (Hoehn and Yahr score), MMSE Score (Mini-Mental State Examination score). Data represent the mean ± 1 standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease (n=6)</th>
<th>Parkinson’s disease related dementia (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.2 ± 7.9</td>
<td>72.9 ± 6.0</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>5/1</td>
<td>4/3</td>
</tr>
<tr>
<td>Disease duration</td>
<td>10.5 ± 4.1</td>
<td>12.4 ± 5.3</td>
</tr>
<tr>
<td>H&amp;Y score</td>
<td>2.6 ± 0.4</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.3 ± 1.0</td>
<td>21.3 ± 2.3*</td>
</tr>
</tbody>
</table>

* statistically significant difference P<0.05.

than in the PD group (P<0.001). A selection of the SPM data is presented as maximum intensity projections in Figure 9.1. No areas with a significant increase in $[^{123}I]$Iododexetimide binding were detected within the brains of PDD patients as compared to PD patients. However, a significant decrease in tracer binding in the PDD group as compared to the

Figure 9.1. Selection of the SPM analysis results. Left panel: Maximum intensity projections in three orthogonal planes ($p_{uncorrected} \leq 0.005$ and $k \geq 50$ voxels). Right panel: Statistically significant decrease of $[^{123}I]$Iododexetimide binding in temporal cortex (superimposed upon the summed obtained SPECT scans). a Left inferior temporal cortex $p_{uncorrected} < 0.001$; b Left inferior temporal cortex $p_{uncorrected} < 0.001$; c Left superior temporal cortex $p_{uncorrected} < 0.001$; d Right Left superior temporal cortex $p_{uncorrected} = 0.002$. See color figure appendix.

PD group was detected in several cortical areas. Decreases were detected in both the left temporal lobe (inferior temporal cortex area $p_{uncorrected} < 0.001$, hippocampus area $p_{uncorrected} < 0.001$) and the right temporal cortex (inferior temporal cortex $p_{uncorrected} < 0.001$, superior temporal cortex $p_{uncorrected} < 0.001$). Additionally, a decrease of $[^{123}I]$Iododexetimide binding was revealed in the posterior cingulate area in the left ($p_{uncorrected} < 0.001$) and the right ($p_{uncorrected} = 0.001$) cerebrum.

Discussion

The present study demonstrates a significant decrease of in-vivo $[^{123}I]$Iododexetimide binding, likely reflecting decreased muscarinic receptor
availability, in both superior and inferior temporal cortical areas, the left hippocampal area and posterior cingulate area in PDD as compared to PD patients.

Colloby et al. recently reported on muscarinic receptor availability in patients suffering from Lewy body dementia, PDD, and controls using the muscarinic M1/4 radiotracer \([^{123}\text{I}]\text{QNB}\) and SPECT. In that study, a significantly lower binding was detected in the medial temporal lobe of PDD patients as compared to controls. The results of our study are in line with those observations, since we showed decreases in the temporal cortex areas bilaterally in PDD versus PD patients. Moreover, in a previous study we also showed loss of \([^{123}\text{I}]\text{Iododextimide}\) binding in the left temporal cortex of early AD patients. In agreement with our present findings, a postmortem study by Perry et al., demonstrated loss of choline acetyltransferase (marker for cholinergic activity) in the temporal cortex of PD(D) patients which correlated with the severity of dementia. Unfortunately, the size of the present study group did not permit regression analysis to evaluate a potential correlation between \([^{123}\text{I}]\text{Iododex-

etimide}\) binding in the temporal cortical areas and MMSE scores.

Although the superior and inferior temporal cortex and the hippocampus are well recognized brain areas involved in memory function, the posterior cingulate gyrus may also play a critical role in memory. For example, and in line with our finding, a recent spectroscopy study showed lower N-acetylaspartate/creatine (NAA/Cr) in the posterior cingulate gyrus of PDD patients compared with controls and compared with non-demented PD patients.

In the abovementioned study, an increase of muscarinic receptor binding was detected in the occipital cortex of both the DLB and PDD patients as compared to controls. Presently, we did not observe such an increase of binding in PDD versus PD patients. It is possible, however, that the increase of binding is also present in PD patients. Since we compared PDD patients directly to PD patients, we may be unable to reproduce increased tracer binding in the occipital cortex in PDD and/or PD patients.

To reduce the duration of the SPECT acquisition to 40 min (which was considered a maximum for patients with dementia), we have chosen to obtain partial brain scans, neglecting data from the upper part of the parietal and frontal cortices and the cerebellum. Differences in tracer uptake could therefore not be determined in these brain areas which is a limitation of the present study. Additionally, the small diameter of the head port of our dedicated brain SPECT camera complicated positioning...
of the head in the gantry, and caused deviation from the orbitomeatal line in some patients, although this was corrected by matching of the data sets to the T1 MNI template.

The present data were not corrected to account for possible differences in regional cortical atrophy and perfusion between the two study groups. Regional atrophy in cortical areas including the temporal cortex in both PD and PDD as compared to controls has been reported previously in some studies, but the exact location of atrophy varies among these reports. According to the study by Burton and co-workers\textsuperscript{10}, regional atrophy in PDD relative to PD is present predominantly in the occipital cortex but not in the temporal cortex, hippocampus or the posterior cingulate area. Relative to this study, it seems unlikely that our results can be fully attributed to regional atrophy, since we detected differences in tracer binding in areas outside the occipital cortex. On the other hand, some effects of global or regional cortical atrophy due to ageing or as a characteristic of the disease, on the results of our study cannot be excluded.

In conclusion, the present study demonstrates decreased muscarinic receptor binding in the temporal cortical and the posterior cingulate areas in PDD versus PD. The findings suggest that reduced muscarinic receptor binding in these brain areas could be used as a marker for PDD. Additionally, in-vivo $[^{123}\text{I}]$Iododexetimide SPECT-imaging might be of value for the selection of PDD patients that are likely to respond to AChEIs.

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**References**


