Dopamine transporter imaging under high-dose transdermal nicotine therapy in Parkinson’s disease: an observational study
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Objectives Nicotine therapy might improve the course of Parkinson's disease. This observational study evaluated the performance of dopamine transporter imaging in follow-up patients under nicotine therapy.

Methods Six Hoehn and Yahr stage III patients underwent 123I-FP-CIT imaging prior to, 3 months, and 1 year after the onset of nicotine therapy. Nicotine was administered transdermally with increasing daily doses during 3 months (up to 105 mg/day) and decreased progressively. On co-registered magnetic resonance imaging, striatal regions of interest were drawn and binding potentials of 123I-FP-CIT were calculated. Changes in Unified Parkinson’s Disease Rating Scale-III over time were compared with binding potentials using regression analysis.

Results All patients improved motor scores at 3 months (−65 ± 22% ‘off’, −89 ± 12% ‘on’) and most received fewer dopaminergic drugs (−30% dosage in average). Motor improvement persisted to a lesser extent at 1 year (−39 ± 31% ‘off’, −13 ± 43% ‘on’), partly because one patient stopped the treatment. Interestingly, the decrease in binding potentials (−4.0 ± 10.5%) was slower than that expected in Parkinsonian patients (usually −10% per year) and was inversely correlated with Unified Parkinson’s Disease Rating Scale-III improvement, $r=0.83$ ‘off’ and 0.91 ‘on’.

Conclusion This observational study emphasizes a potential effect of nicotine therapy on striatal dopamine transporter density, which may be interpreted as direct pharmacological effect or deceleration of neuronal loss. Nucl Med Commun 30:513–518 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: binding potentials, dopamine transporter imaging, neuroprotection, nicotine, Parkinson’s disease

Introduction Transdermal nicotine therapy has been proposed as a potential alternative to dopaminergic drugs in Parkinson’s disease (PD), because epidemiological studies have shown that the incidence of PD is lower in smokers [1]. Indeed, nicotine is thought to stimulate striatal dopamine neurons and to protect against neuronal insult, as suggested by several case reports [2,3]. Besides, in a recent open-label trial, we observed that high-dose transdermal nicotine improved motor scores after 17 weeks of therapy and allowed reduction of the dosage of dopaminergic drugs in six patients with Hoehn and Yahr stage III idiopathic PD [4].

However, the mechanisms of action of nicotine over the nigrostriatal pathway remain unclear and functional imaging of dopaminergic neurotransmission could help determine whether nicotine stimulates dopamine release in the striatum or has a neuroprotective – or even a neurotrophic – effect. This study sought to evaluate the long-term effect of high-dose transdermal nicotine therapy on striatal presynaptic function, using dopamine transporter imaging with $N$-o-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ($^{123}$I-FP-CIT) single-photon emission computed tomography (SPECT), in the six patients reported above [4].

Methods Study protocol Six patients, all men, aged 55.7 ± 3.3 years, with Hoehn and Yahr stage III idiopathic PD, were enrolled into a prospective open-label trial designed to assess the long-term feasibility and tolerance of high-dose transdermal nicotine therapy [4]. Idiopathic PD diagnosis was made...
according to the United Kingdom Parkinson’s Disease Society Brain Bank criteria [5]. Patients had no history of smoking, psychiatric disease, including dementia, and no contraindication for nicotine therapy, including cardiac, hepatic, or renal conditions. Their treatment consisted of an association of L-dopa, either L-dopa+benserazid ($n = 5$) or L-dopa+carbidopa ($n = 1$), with the dopaminergic analog pergolide ($n = 6$). They were not treated with psychostimulants or antidepressants; that is, drugs that may interfere with dopamine transporter imaging. The study was approved by our institutional review board and written informed consent was obtained from each patient.

Patients received transdermal nicotine (Nicorette; Pfizer, Paris, France) and were followed up for 29 weeks. Nicotine doses were gradually increased from 5 to 105 mg/day during 14 weeks, maintained at the maximum during 3 weeks, then gradually decreased during 8 weeks, and maintained at 0 mg/day for the last 4 weeks. After the end of the trial (30th week), five patients asked expressively to continue the treatment, at their own expense, with an average nicotine dosage of 45 mg/day, whereas the last patient had complete withdrawal of nicotine. All patients had general and neurological examinations at least 10 times during the protocol; ‘on’ and ‘off’ Unified Parkinson’s Disease Rating Scale-III (UPDRS-III) scores were also measured prior to, 3 months, and 1 year after the onset of treatment.

**Imaging procedure**

Brain magnetic resonance imaging (MRI) was performed in all patients during the week preceding the onset of treatment, on a 1.5 T scanner (Symphony; Siemens Medical Solutions, Munich, Germany). T2-weighted spoiled gradient echo images were obtained (flip angle = 15°, repetition time = 5500 ms, echo time = 101 ms, field of view = 187 × 250 mm, matrix = 192 × 256 pixels) to cover a volume from the skull base to the vertex with approximately 45 contiguous, 3-mm-thick transaxial slices.

In addition, dopamine transporter imaging was performed in all patients prior to, 3 months (week 14, maximal nicotine dosage), and 1 year after the treatment onset, on a dual-headed γ-camera (Axis; Philips Medical Systems, Paris, France) equipped with high-resolution, parallel-hole collimators. SPECT acquisition started 3 h after intravenous injection of 150–170 MBq $^{123}$I-FP-CIT (DaTSCAN; GE HealthCare, Little Chalfont, UK), and consisted of four consecutive 180° circular orbits (for a total of 120 projections, 20 s/projection after summation, matrix 128 × 128). Images were reconstructed using an iterative algorithm, post-filtered with a low-pass Butterworth (order 4, cutoff 0.35 cycles/pixel), and attenuation corrected by the Chang method to obtain transaxial volumes (pixel size 2.3 × 2.3 × 2.3 mm³).

**Data analysis**

For each patient, the three transaxial SPECT volumes and the MRI volume were segmented to extract the brain surfaces using a semiautomatic thresholding associated with mathematical morphology erosion and dilatation processes [6]. Brain surfaces were then co-registered using a Powell-based rigid-body affine function with 6 degrees of freedom and reoriented SPECT volumes were resliced according to the MRI orientation [6]. Then, manual volumes of interest were drawn on the MRI slices by an experienced physician around the caudate nuclei, the putamen nuclei, and the occipital cortex. Volumes of interest were automatically propagated on the co-registered SPECT volumes and radioactive counts were obtained (Fig. 1). Binding potentials (BPs) of $^{123}$I-FP-CIT were calculated for each basal ganglia (caudate and putamen, right and left) using the following formula [7]: BP = basal ganglia/occipital counts – 1.

BP values were normalized to the mean striatal value (BP = 2.52) obtained in a population of 10 controls presenting an essential tremor [8]. Then, percentages of BP difference were calculated between pretherapeutic and 3-month scans, and between pretherapeutic and 1-year scans. Concurrently, percentages of UPDRS-III difference were calculated between the same periods, and linear regression analysis was performed between changes in BP and UPDRS-III values over time. Comparisons of contiguous variables (clinical and imaging data) between pretherapeutic assessment and later assessments, at 3 months and 1 year, were done using paired Students $t$-test ($P < 0.05$ indicated significance).

**Results**

Patient characteristics and imaging results are shown in Table 1. All patients had severe motor impairment as shown by the high UPDRS-III scores ‘off’ (ranging 48–77) and ‘on’ (ranging 13–24), before the onset of nicotine therapy. After 3 months, at maximal nicotine dose, motor function significantly improved as shown by a marked reduction of UPDRS-III scores ‘off’ (range 0–36, mean reduction $–65 \pm 22\%$) and even more ‘on’ (range 0–5, mean reduction $–89 \pm 12\%$). After 1 year, UPDRS-III scores ‘off’ remained significantly lower than at baseline, although to a lesser extent (range 22–60, mean reduction $–39 \pm 31\%$), whereas UPDRS-III ‘on’ showed only a trend for reduction (range 9–20, mean reduction $–13 \pm 43\%$), partly because one patient developed side effects and did not continue nicotine treatment (UPDRS-III ‘off’ = 60, ‘on’ = 20).

The beneficial effects of nicotine treatment appeared only after 7 weeks with a dose higher than 45 mg/day, as reported earlier [4]. As a consequence, the dosage of L-dopa and dopamine agonists (expressed in L-dopa equivalent dose, see Table 1) could be reduced by...
– 29 ± 40 and –31 ± 25%, respectively, after 3 months and 1 year of nicotine treatment onset. All patients but one tolerated up to 105 mg/day of nicotine, one patient needed a dose reduction when he reached 105 mg/day, and then received 75 mg/day (investigator’s decision). Adverse events occurred between 90 and 105 mg/day; they were very common but moderate, consisting of nausea, insomnia, and hypotension, and could be corrected with symptomatic treatments.

On imaging, all patients presented a marked, posterior-to-anterior, and asymmetrical dopaminergic loss, a typical pattern for Hoehn and Yahr stage III idiopathic PD. Raw BP values ranged between 0.47 and 1.93 and were usually higher on the caudate (1.33 ± 0.27) than on the putamen (1.11 ± 0.48, \( P < 0.05 \)). When expressed as normalized values, pretherapeutic caudate and putamen BPs averaged 49.2 ± 9.2 and 35.3 ± 10.3% of the control value (BP = 2.52), respectively, on the most impaired side. After 3 months and 1 year of nicotine therapy, BP values remained remarkably stable with less than 5% decrease over time, −1.3 ± 8.2 and −4.0 ± 10.5%, respectively. Statistically, the evolution of BP values between pretherapeutic and later scans was not significant, with \( P \) values ranging between 0.22 and 0.99. When excluding the patient who did not tolerate the treatment and needed a nicotine dosage reduction, BP values were even more stable, +1.8 ± 3.5 and −0.7 ± 7.3% at 3 months and 1 year, respectively.

Regression analysis between the evolution of UPDRS III scores and BP values (average of caudate and putamen) from baseline to 3 months did not show any significant
relationship. In contrast, regression analysis at 1 year showed an inverse relationship between the evolution of UPDRS III scores and BP values, with $r = 0.83$ 'off' and $r = 0.91$ 'on' (Fig. 2). In other words, BP reduction was less pronounced in patients who improved their UPDRS III scores the most and was more pronounced in the one patient who did not benefit from nicotine treatment. When considering each striatal nucleus separately, it was noted that this inverse relationship was present both on the caudate and the putamen and both on the most impaired side and the less impaired side, with $r$ coefficients ranging between 0.54 and 0.99.

**Discussion**

This observational study in a small series of PD patients emphasizes a potential effect of nicotine therapy on striatal dopamine transporter density, which may be interpreted as a direct pharmacological effect or deceleration of neuronal loss.

Dopamine transporter imaging is a powerful biomarker used to measure disease severity in patients with PD. Visual image interpretation relies on a three-grade scale reflecting the neurobiological process of nigrostriatal degeneration, that is, posterior-to-anterior and bilateral, but asymmetrical [9,10]. In addition, this imaging technique allows an easy and reproducible semiquantification of radiotracer binding to its receptor, inherited from positron emission tomography, by means of regions of interest drawing [7,11]. Using dopamine transporter imaging, several studies have shown that striatal dopaminergic loss over time is a little above 10% per year in PD patients, whereas it is a little below 1% per year in healthy controls [11,12]. In our series, although we found a slight decrease of dopamine transporter BPs over time (averaging −4% per year), this does not reach the expected −10% per year reported earlier, suggesting deceleration of the pathological process under nicotine therapy. When considering the five patients who followed the treatment correctly, BP reduction was less than 1% per year (averaging −0.7% per year), which compares well with that published in healthy controls. Most importantly, the deceleration of BP decrease after 1 year of treatment onset was significantly correlated with the improvement in motor scores, whereas such a correlation was not found earlier in the course of treatment (at 3 months); this suggests that the beneficial effect of nicotine is not only a direct short-term effect on symptoms relief but might persist in the long term.

**Table 1** Clinical characteristics and dopamine transporter imaging results

<table>
<thead>
<tr>
<th></th>
<th>Pretherapeutic</th>
<th>3 months</th>
<th>1 year</th>
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<tbody>
<tr>
<td><strong>UPDRS III score</strong></td>
<td></td>
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<tr>
<td>'Off' treatment</td>
<td>58.2 ± 11.0</td>
<td>20.3 ± 13.0*</td>
<td>34.2 ± 14.4*</td>
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<tr>
<td>'On' treatment</td>
<td>17.5 ± 4.4</td>
<td>2.3 ± 2.6*</td>
<td>14.0 ± 4.8**</td>
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<tr>
<td>L-dopa equivalent dose (mg/day)</td>
<td>20.3 ± 13.0*</td>
<td>34.2 ± 14.4*</td>
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<tr>
<td><strong>Basal ganglia volumes (ml)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Caudate – more impaired side</td>
<td>4.84 ± 0.78</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Caudate – less impaired side</td>
<td>4.83 ± 0.79</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Putamen – more impaired side</td>
<td>4.51 ± 0.35</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Putamen – less impaired side</td>
<td>4.44 ± 0.29</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Normalised binding potentials (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate – more impaired side</td>
<td>49.2 ± 9.2</td>
<td>47.3 ± 8.8**</td>
<td>45.0 ± 8.9**</td>
</tr>
<tr>
<td>Caudate – less impaired side</td>
<td>56.4 ± 11.6</td>
<td>56.3 ± 10.4**</td>
<td>52.5 ± 12.4**</td>
</tr>
<tr>
<td>Putamen – more impaired side</td>
<td>35.3 ± 10.9</td>
<td>36.1 ± 10.9**</td>
<td>31.2 ± 8.7**</td>
</tr>
<tr>
<td>Putamen – less impaired side</td>
<td>52.7 ± 22.2</td>
<td>48.7 ± 16.4**</td>
<td>48.6 ± 16.3**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
Paired $t$-test compared with pretherapeutic evaluation: *$P \leq 0.01$, **$P > 0.05$ (NS).
UPDRS, Unified Parkinson’s Disease Rating Scale.

Regression analysis between changes in binding potentials (average of caudate and putamen) and changes in Unified Parkinson's Disease Rating Scale-III (UPDRS-III) scores 'off' (a) and 'on' (b), after 1 year of nicotine therapy. Dotted curves represent the 95% confidence interval limits.
The effect of nicotine on nigrostriatal pathway is not completely understood. Nicotine acts as an agonist of nicotinic acetylcholine receptors, mainly the α2-6 subunits, which are present on the terminals of dopaminergic neurons and, therefore, can regulate dopamine release in the striatum [13]. This modulatory effect may be used to reduce Parkinson symptoms, as it has been shown in Parkinsonian monkeys that co-administration of a nicotinic agonist with a lower l-dopa dosage results in a reduction of symptoms similar to that seen with higher l-dopa dosage [14]. As a matter of fact, in this study, we were able to reduce l-dopa and dopamine agonist dosages by approximately –30%, concurrently with the increase of nicotine dosage during the first 3 months of the study, without worsening of symptoms, and, in contrast, with a continuous improvement of motor scores. This finding is of paramount importance because l-dopa is suspected to have a toxic effect on striatal terminals, and a therapeutic strategy allowing reduction of l-dopa dosages would be highly beneficial to PD patients [15].

Moreover, there is some evidence in the literature that the modulatory effect of nicotine on nigrostriatal neurons may protect against disease progression. Indeed, chronic nicotine treatment has been shown to protect dopaminergic neurons in monkeys against the damage induced by the selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [16]. It is hypothesized that by increasing tyrosine hydroxylase activity, vesicular monoamine transporter and dopamine transporter in the striatal terminals, the high dopamine release induced by nicotine competes with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine which, then, cannot concentrate and leads to nerve terminal degeneration. Ultimately, nicotine may protect against neuronal injury in the substantia nigra by preventing overactivation of the neighboring microglia, which consists of mononuclear phagocytes, by inhibiting the release of tumor necrosis factor-α through the nicotinic acetylcholine receptor α7 subunit [17], or even stimulate neuronal regeneration through the brain-derived neurotrophic factor [18].

Several study limitations must be pointed out. First, our series has no control group of PD patients not treated with nicotine to compare the evolution of BPs over time. However, the decrease of striatal uptake by more than 10% per year in PD patients has already been published with dopamine transporter imaging [12]. Although the slope linearity of neuronal loss is debated when assessed by 18F-dopa [19], our results, obtained with 123I-FP-CIT, indicate a relative stabilization of striatal uptake which is not expected to result from enzymatic upregulation mechanisms in at least the five patients who maintained nicotine therapy. The last patient, in whom a reduction of nicotine therapy was decided for tolerance issues and who did not continue the treatment after the 30th week, represents the only ‘control’ of our series. As a matter of fact, this patient had profound alteration of BPs over time, as well as degradation of motor scores (higher extremes of Table 1): putamen BPs decreased from 1.93 (77% of the normal value), on pretherapeutic scan, to 1.27 (50%) at 3 months and to 1.09 (43%) at 1 year on the less impaired side, and decreased from 0.99 (39%) to 0.72 (29%) and to 0.59 (23%), respectively, on the more impaired side. This observation further sustains the hypothesis that both chronic and high-dose nicotine administration is necessary to obtain beneficial effect [4]. It may also be hypothesized that not all PD patients equally respond to nicotine therapy.

Finally, 123I-FP-CIT uptake may be affected by interfering medications. Indeed, psychostimulants such as cocaine and amphetamine agonists are known to reduce striatal uptake of 123I-FP-CIT by competition [20], whereas serotonin reuptake inhibitors are known to increase it by displacement from the serotonin transporter [21]. However, patients in our study were naïve with regard to these drugs and were treated only by usual dopaminergic medications, which are reported not to affect the striatal uptake of 123I-FP-CIT [22].

To conclude, although our data are limited, this preliminary report emphasizes, using dopamine transporter imaging, a relative stabilization of striatal neuronal density in PD patients after high-dose transdermal nicotine therapy, suggesting either a pharmacological effect or a neuroprotective effect. Larger, placebo-controlled series are necessary to explore these hypotheses.

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