Chronic high dose transdermal nicotine in Parkinson’s disease: an open trial


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Whether nicotine has therapeutic effects on Parkinson’s disease (PD) symptoms is controversial, but high doses and chronic treatment have never been tested. We report the results of a pilot, open-label trial to assess the safety and possible efficacy of chronic high doses of nicotine. Six patients with advanced idiopathic PD received increasing daily doses of transdermal nicotine up to 105 mg/day over 17 weeks. All patients but one accepted the target dose. Nausea and vomiting were frequent but moderate, and occurred in most of the patients (four of six) who received over 90 mg/day and 14 weeks of nicotine treatment. During the plateau phase, patients improved their motor scores and dopaminergic treatment was reduced. These results confirm the feasibility of chronic high dose nicotinic treatment in PD but warrant validation of the beneficial effects by a randomized controlled trial.

Introduction

Parkinson’s disease (PD) motor symptoms are treated by Levodopa and dopaminergic agonists [1]. Following the observation of an inverse relationship between cigarette smoking and PD [2], the administration of nicotine has been proposed as a treatment for PD, but its mechanism of action and therapeutic efficacy remain controversial [3]. Previous case studies suggested that parkinsonian symptoms were relieved following nicotine patch application [3,4]. Three controlled studies yielded contradictory results: one study reported a worsening of motor symptoms [5], another concluded that there was no effect [6] and the third found motor and cognitive improvements [7]. A recent prospective, open-label trial with increasing doses over 25 days resulted in 59% discontinuation of drug because of side effects and neither improvement nor worsening of motor and cognitive symptoms in the remaining nine subjects [8]. We have previously reported a single case of PD who experienced a major improvement following 3 years of high dose nicotine administration [4,9]; today this patient has received this treatment for 6 years, with good clinical efficacy, and no cardiac and vascular safety concerns. Therefore, a pilot trial was designed to (i) assess the safety of chronic treatment with high doses of transdermal nicotine, (ii) screen a target dose in terms of safety/efficacy ratio and (iii) select follow-up variables with a view to a future randomized, placebo-controlled trial.

Patients and methods

Patients

Ethical approval and permission was provided by the ethics committee of the Pitié-Salpêtrière Hospital. Six non-demented patients with Hoehn and Yahr stage III (in ‘ON’ condition) idiopathic PD were recruited and gave written informed consent. The clinical diagnostic was made according to the criteria proposed by the United Kingdom Parkinson’s disease Society Brain Bank [10]. All patients were never smokers. Exclusion criteria were: a history of cardiac, hepatic, renal or psychiatric disease, age >70 or <40 years, weight >90 kg or <60 kg, hypertension, condition not suitable for transdermal nicotine treatment. The clinical characteristics of these six male subjects were as follows: age: 55.7 ± 3.3 years; disease duration: 7.6 ± 3.2 years; daily dose of l-Dopa 433 ± 150 mg and daily dose of pergolide 4.8 ± 1.0 mg; ‘OFF’ unified Parkinson’s disease rating scale (UPDRS) motor score: 58.2 ± 11.0.

Treatment protocol

All subjects received increasing daily doses of nicotine over 14 weeks (week 1–14 and dose 5–105 mg/day). They were maintained at the highest tolerated dose for...
4 weeks (up to week 17), after which the dose was gradually decreased until week 29. Nicotine was supplied to the patients by adhesive transdermal patches (Nicorette®; Pharmacia, Uppsala, Sweden) containing respectively 8.3, 16.6 and 24.9 mg of nicotine. This type of patch is worn over a 16 h-period, during which the nicotine release is 5, 10 and 15 mg respectively; during the trial, patches were worn 24 h, and removed daily. The patches were placed on the lower abdominal, lumbar or back skin. Follow-up included 10 visits with general and neurological examination (with full UPDRS scale), five phone calls to record adverse events (AE), five psychiatric examinations, five cardiac examinations (with ECG), five acute L-Dopa tests. Urinary assays of cotinine were performed to examine compliance with patch dosing. When AE occurred, the investigator was allowed to decrease nicotine dose, then the last dose was maintained until the period of decrement. Severity of AE was recorded according to the world health organization adverse reaction terminology (WHO-ART) classification.

Statistical analysis

The results are expressed as arithmetic means with the standard deviation or as percentages. Statistical comparisons were made using McNemar’s test for percentages and Wilcoxon’s test for means. *P*-values <0.05 were considered statistically significant. All statistical analyses were conducted using the spss 12.0 (SPSS, Chicago, IL, USA) package for Windows.

Results

Adverse effects

All patients but one accepted up to 105 mg/day until week 17, one needed a reduction of dose when he reached 105 mg/day, and received then 75 mg/day (investigator’s decision). Three patients reported minor itching between week 6 and 10, with spontaneous recovery after moving the placement of patches. Nausea, vomiting, orthostatic hypotension and insomnia were common AE of both nicotine and L-Dopa. Figure 1 shows the evolution of AE according to the protocol duration and the nicotine dose. All AE were moderate throughout the study except orthostatic hypotension in one patient at 75 mg/day at week 10. Nausea and vomiting were frequent (four of six patients), occurring predominantly between week 17 (105 mg/day) and week 20 (90 mg/day), and disappearing thereafter. Insomnia (3/6) and orthostatic hypotension (6/6) occurred during the treatment period but had already been observed at baseline in three and five patients respectively. Three patients reported irritability at week 10 (75 mg/day), which improved later. Symptomatic treatments of AE were already planned in the protocol and given: 3/6 patients received domperidone, 5/6 midodrine and 6/6 diazepam. No significant difference in blood pressure (BP) (but a trend to elevated BP) and heart rate between week 17 and baseline (Table 1) or other cardiac effects during treatment were observed. No significant difference in drug AE was observed between baseline and any time during treatment. A trend was observed between baseline and week 17 for red cells (4.8 ± 0.15 vs. 4.7 ± 0.12, *P* = 0.09), haematocrit (44.5 ± 2.1 vs. 42.8 ± 1.2, *P* = 0.07) and monocytes (6.3 ± 1.4 vs. 7.3 ± 1.4, *P* = 0.10).

Figure 1 Scores of unified Parkinson’s disease rating scale (UPDRS) ON total (●) and III (■) and urinary cotinine concentration (▲) during treatment periods (mean and 95% confidence interval). There was a correlation between urinary cotinine and UPDRS III ‘ON’ (Spearman coefficient = -0.55 *P* < 0.001, *n* = 49), and with total UPDRS score (Spearman coefficient = 0.59 *P* < 0.001, *n* = 44). A significant effect on ‘ON’ UPDRS scores was observed, starting from week 7/45 mg/day (7.8 ± 5.8, *P* = 0.03) to week 20/95 mg/day (4.7 ± 3.0, *P* = 0.03), as compared with baseline (17.5 ± 4.4).
Table 1 Patient characteristics at baseline and after 17 weeks of treatment

<table>
<thead>
<tr>
<th>Safety</th>
<th>Baseline</th>
<th>Week 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>117.5 (10.2)</td>
<td>132.2 (9.2)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>69.8 (5.1)</td>
<td>78.7 (7.7)</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘ON’ H &amp; Y score</td>
<td>3.0 (0.0)</td>
<td>2.2 (1.0)</td>
</tr>
<tr>
<td>Cotinine (µM)</td>
<td>6.4 (1.4)</td>
<td>250.6 (57.2)*</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3.5 (1.4)</td>
<td>0.0 (0.0)*</td>
</tr>
<tr>
<td>II</td>
<td>6.8 (4.0)</td>
<td>0.5 (0.8)*</td>
</tr>
<tr>
<td>III</td>
<td>17.5 (4.4)</td>
<td>3.8 (2.1)*</td>
</tr>
<tr>
<td>IV</td>
<td>6.2 (4.0)</td>
<td>0.0 (0.0)*</td>
</tr>
<tr>
<td>Total</td>
<td>34.0 (7.5)</td>
<td>3.5 (2.9)*</td>
</tr>
</tbody>
</table>

*All patients received pergolide in this cohort.

*P < 0.05.

BP, blood pressure; UPDRS, unified Parkinson’s disease rating scale.

Motor improvement

All patients improved their motor scores and most required less dopaminergic drugs (Table 1). There was a correlation between motor improvement and urinary excretion of cotinine (Fig. 1). Following the end of the trial, all the patients asked for continuation of treatment with nicotine. An improvement of ‘ON’ UPDRS scores was observed, starting from week 7/45 mg/day (7.8 ± 5.8, P = 0.03) to week 20/95 mg/day (4.7 ± 3.0, P = 0.03), as compared with baseline (17.5 ± 4.4). L-Dopa intake was reduced at week 26 (270 ± 152 mg, P = 0.04) and week 29 (230 ± 139 mg, P = 0.04) compared with baseline (433 ± 150 mg). Similar results were observed for pergolide with 4.8 ± 1.0 mg at baseline versus 2.7 ± 1.3 mg at week 26 (P = 0.04), suggesting a delay in nicotine action.

Discussion

The finding that there is an inverse and dose-dependent relationship between tobacco consumption and prevalence of PD in prospective studies argues for the use of nicotine to treat PD [7]. Most prospective placebo-controlled clinical trials have found a lack of efficacy of nicotine treatment on PD [5,6,8], only one reporting a clinical improvement [7]. However, our trial differs by (i) the long duration of treatment and (ii) the very high daily doses of nicotine. Drug AE mostly occurred at doses between 90 mg/day and 105 mg/day. They were very common but remained moderate, and could be managed with drugs to correct nausea, insomnia and hypotension. Systolic and diastolic BP increased at week 17, and this need to be assessed in future trials.

A possible beneficial effects of nicotine treatment appeared only after 7 weeks with a dose >45 mg/day. These results observed on six patients show that chronic treatment with high doses of nicotine may be tolerated and suggest that the most efficient dose is between 45 mg/day and 90 mg/day. The dosage must be progressive, starting at 5 mg/day, and slowly incremented. After >6 years a single subject with idiopathic PD still accepts >100 mg/day without side effects [9], and without BP change. Being tolerated, this treatment may improve motor performance and decrease dopaminergic requirement. It may be argued that the small size of this cohort, and the open-label design of this trial do not allow us to rule out a placebo effect. Namely, the major improvement of total UPDRS scores may be explained by (i) the simultaneous occurrence of motor, and cognitive improvement (UPDRS I), leading to an improvement of depressive symptoms, (ii) by the enthusiasm of patients in participating to this trial and (iii) the open-label design of the trial, with a very small cohort of patients. However several indications of possible symptomatic improvements must be taken into account: (i) the occurrence of UPDRS improvements when the urinary excretion of cotinine was elevated, suggesting an active effects of nicotine and (ii) the fact that the improvement was maintained despite the reduction of dopaminergic drug intake. If real, the beneficial effects may be explained by a direct effect of nicotine on the central nervous system, mediated either by nicotinic receptors in the dopaminergic pathways [11], or possibly by a neuroprotective/neurotrophic effect [2,12], or a D3 receptor upregulation which improves endogenous or exogenous dopamine use [13]. These hypotheses may be related to the need for chronic and high dose treatment, but must be tested by quantitative imaging methods. In conclusion, the results of this pilot study indicate that a long-term, high dose treatment of PD with transdermal nicotine is feasible. However, the beneficial effect remain to be validated by a randomized, controlled, phase II trial.

Author contributions

GV was the first investigator. CB, AR, SB and SA participated in the investigation. PC initiated the study and wrote the manuscript. JH acted as a consultant and wrote the manuscript. IM-M organized the study. PM designed the protocol, analysed the data and wrote the manuscript.
Conflict of interest

J. Le Houezec has worked as scientific advisor for a nicotine replacement therapy producing company not involved in the study.

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References