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Amantadine improves gait in PD patients with STN stimulation

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ABSTRACT

In advanced Parkinson's disease (PD), axial symptoms such as speech, gait, and balance impairment often become levodopa-unresponsive and they are difficult to manage, even in patients with subthalamic nucleus deep brain stimulation (STN-DBS). We anecdotally observed that oral administration of amantadine was very effective in treating both residual and stimulation-induced axial symptoms after bilateral STN-DBS in one PD patient. Therefore, we conducted a prospective multicenter observational study to evaluate the effects of amantadine on speech, gait and balance in PD patients with STN-DBS and incomplete axial benefit. Primary outcomes were changes in speech (UPDRS III, item 18), gait (item 29) and postural stability (item 30) with amantadine treatment compared to baseline. Secondary outcome was the patients' subjective scoring of axial symptoms with amantadine compared to baseline. Forty-six PD patients with STN-DBS were enrolled in the study and followed for 10.35 ± 8.21 months (median: 9.00; range: 1–31). The mean daily dose of amantadine was 273.44 ± 47.49 mg. Gait scores significantly improved (from 1.51 ± 0.89 to 1.11 ± 0.92, $P = 0.015$) with amantadine treatment, whereas postural stability and speech scores were similar before and after treatment. Thirty-five (76.1%) patients reported subjective improvement in speech, gait or balance with amantadine, whereas thirty (65.2%) patients reported improvement in gait and balance. In conclusion, our data suggest that amantadine may have new beneficial effects on axial symptoms in PD patients with STN-DBS.

1. Introduction

In patients with advanced Parkinson's disease (PD), speech, gait and balance disorders often become poorly responsive to levodopa and they are very difficult to manage, thus resulting in severe disability and marked reduction in quality of life [1]. Subthalamic nucleus deep brain stimulation (STN-DBS) is effective in improving levodopa-responsive signs in PD patients, particularly tremor, rigidity and bradykinesia, even after long-term follow-up [2–4]. However, the benefits of STN-DBS on motor function seem to gradually diminish over the years [5], possibly reflecting the progressive development of levodopa-resistant speech, balance and gait problems in advanced PD patients [6–9]. Moreover, some axial signs, particularly speech, can also be worsened by high frequency STN-DBS, especially with high-amplitude stimulation [5,8,10].

Amantadine is a nonselective NMDA receptor antagonist that was first described by Schwab et al. [11] to be a potential treatment for PD. It is currently used in the management of different stages of PD [12]. In advanced PD, amantadine is mostly utilized to treat peak-dose levodopa-induced dyskinesias [13,14]. Its antidyskinetic effect has recently been demonstrated by a multicenter double-blind randomized controlled trial [15]. Besides, it has also been used to treat gait disorders, with conflicting results. In a double-blind study conducted by the King's College group in London in 1970, amantadine hydrochloride resulted in a significant improvement in gait [16]. Two more recent studies also suggested that amantadine may be useful in treating levodopa-unresponsive freezing of gait in PD patients [17,18]. In contrast, Macht et al. reported that amantadine users were more likely to develop freezing of gait [19]. A benefit of amantadine on speech disorders in PD patients has not been documented. In 2009, we anecdotally

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observed that the introduction of amantadine to treat levodopa- and stimulation-resistant axial symptoms in one PD patient with bilateral STN-DBS was very effective. Interestingly, amantadine was much more beneficial than when it was tried before DBS surgery. To our knowledge, no similar studies have reported the effects of amantadine on axial symptoms in PD patients who have undergone STN-DBS. Therefore, we conducted a prospective multicenter study to examine amantadine effectiveness on speech, balance and gait disturbances in STN-DBS PD patients.

2. Patients and methods

This was a prospective multicenter open observational study, involving three movement disorders surgical centers (Canada, Argentina and Malaysia). Patients were recruited between 2009 and 2010 and followed prospectively. Inclusion criteria were: patients who had undergone STN-DBS surgery for advanced PD, and presence of disabling axial signs (i.e., speech, gait or balance problems) despite optimized stimulation parameters (including trials with low-frequency stimulation) [20,21] and medical treatment. Concerning the latter, all patients had an increase of levodopa and/or dopamine agonists treatment up to the maximal tolerated dosage. When feasible, patients had also a trial with metylphenidate [22] and rasagiline. However, further increase in dopaminergic agents did not improve patients' axial symptoms before the amantadine trial. Exclusion criteria were: PD patients who were treated with amantadine before surgery and still continued it after surgery; patients with dementia and/or major psychiatric issues; or previous intolerance to amantadine.

Amantadine was initiated in a step-wise manner, starting from 100 mg *per os* daily and titrating up to 300 mg daily (depending on its efficacy and side effects) over a few weeks. Other antiparkinsonian medications and stimulation settings remained unchanged during the whole study.

The study was approved by the University Health Network research ethics board. Informed consent was obtained before starting amantadine.

All subjects were evaluated with part III of the Unified Parkinson's Disease Rating Scale (UPDRS III) before (baseline) and after starting amantadine. All evaluations were performed in the on-medication/on-stimulation condition. Patients were also asked to report their subjective opinion of changes in speech, gait and balance at baseline and after starting amantadine. Adverse effects of amantadine treatment were recorded.

2.1. Statistical analysis

Primary outcome measures included changes in speech (UPDRS III, item 18), gait (item 29) and postural stability (item 30). Secondary outcome measures were the patients' subjective scoring of speech, gait and balance after starting amantadine, compared to baseline (no change; mild improvement or worsening; moderate improvement or worsening; marked improvement or worsening).

The analysis of the primary and secondary outcome measures was made using the intention-to-treat (ITT) population, which included all patients who had received at least one dose of amantadine. The primary and secondary outcome measures were studied using the dataset at baseline and at the first follow-up visit. The post-amantadine speech, gait, postural stability, combined gait and postural stability, and total UPDRS III scores were compared to the pre-amantadine scores using Wilcoxon Signed Ranks test. The significance level was defined as $P < 0.05$. Statistical analysis was performed using SPSS 11.5 for Windows.

3. Results

Forty-six PD patients with STN-DBS were included in the study (41 patients from Canada, four from Argentina and one from Malaysia). Among these 46 patients, full data were available in 32 patients. Seven patients (6 patients from Canada and one from Argentina) stopped amantadine before the next follow-up visit, whereas the UPDRS III assessments were not available in 7 patients. Baseline demographic and clinical characteristics of the 46 subjects are presented in Table 1.

Forty-five (97.9%) patients had bilateral STN-DBS, whereas one (2.1%) patient had unilateral STN-DBS. Among the 32 subjects with a complete dataset, 23 (71.9%) patients had previously tried and stopped amantadine prior to DBS. None of these patients presented with any benefit on speech, gait or balance from amantadine during the pre-surgical period. Amantadine was started after surgery for various reasons, namely speech, balance and gait issues. Amantadine was initiated 38.91 ± 29.53 (median: 29.50; range: 3–120) months after surgery. The mean daily dose of amantadine was 273.44 ± 47.49 (median: 300; range: 150–300) mg. Most of the patients had their first follow-up visit six to twelve months after starting amantadine. The mean follow-up duration after initiation of amantadine was 10.35 ± 8.21 (median: 9.00; range: 1–31) months.

Table 1
Baseline demographic and clinical characteristics of the ITT population.

Patients (n = 46)	
Age at PD onset (years)	44.42 ± 9.08 (median: 42; range: 25–62)
Gender (male/female), *n*	36/10
Type of PD	
Tremor-dominant	17 (37.0%)
Akinetic-rigid	29 (63.0%)
Age at surgery (years)	57.17 ± 8.51 (median: 58.50; range: 38–71)
UPDRS III score (on-medication/ on-stimulation)	24.64 ± 8.34 (median: 25.00; range: 8–42)
Speech (item 18)	1.85 ± 0.75 (median: 2.00; range: 0–4)
Gait (item 29)	1.51 ± 0.89 (median: 1.00; range: 0–3)
Postural stability (item 30)	1.34 ± 1.06 (median: 1.00; range: 0–4)
Gait and postural stability (items 29 and 30)	2.81 ± 1.73 (median: 2.50; range: 0–7)
Levodopa equivalent daily dosage (mg)	872.87 ± 728.00 (median: 300; range: 0–3750)
Voltage of stimulation (V)	
Right STN	3.15 ± 0.62 (median: 3.40; range: 1.60–4.20)
Left STN	3.20 ± 0.52 (median: 3.35; range: 2.00–4.00)
Pulse width of stimulation (μs)	
Right STN	70.34 ± 22.32 (median: 60; range: 60.00–180.00)
Left STN	63.44 ± 9.52 (median: 60; range: 60.00–90.00)
Frequency of stimulation (Hz)	149.12 ± 37.14 (median: 160.00; range: 50.00–185.00)

3.1. Primary outcome measures

Among the 46 subjects, 14 (30.4%) had a significant improvement in gait scores after starting amantadine treatment (Table 2). Although not significantly improved, a remarkable amelioration of speech after amantadine treatment was seen in some patients (Video, Segments 1 and 2).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2012.11.005.

3.2. Secondary outcome measures

Thirty-five (76.1%) out of 46 patients reported an improvement in axial signs (i.e., either speech or gait and balance, or both) with amantadine. Improvement in gait and balance was reported by 30

Table 2
On-medication/on-stimulation total UPDRS III scores and subscores for speech, gait and postural stability before and after amantadine treatment.

Scores	Pre-amantadine (*n* = 46)	Post-amantadine (*n* = 46)	*P* value
Speech (item 18)	1.85 ± 0.75 (median: 2.00; range: 0–4)	1.64 ± 0.74 (median: 2.00; range: 0–3)	0.20
Gait (item 29)	1.51 ± 0.89 (median: 1.00; range: 0–3)	1.11 ± 0.92 (median: 1.00; range: 0–3)	0.015
Postural stability (item 30)	1.34 ± 1.06 (median: 1.00; range: 0–4)	1.27 ± 0.94 (median: 1.00; range: 0–3)	0.77
Total UPDRS III	24.67 ± 8.34 (median: 25.00; range: 8–42)	23.11 ± 10.30 (median: 25.00; range: 3–42)	0.33