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Beneficial Effects of Amantadine on L-Dopa-Induced Dyskinesias in Parkinson's Disease

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Summary: L-Dopa-induced dyskinesias constitute a challenge to the management of advanced Parkinson's disease. According to recent reports, treatment with the NMDA receptor antagonist amantadine may significantly diminish L-dopa-induced dyskinesias. In the present study, the effect of amantadine on L-dopa-induced dykinesias was assessed in a 5-week, double-blind crossover trial. Dyskinesia severity as assessed following oral L-dopa challenges and by self-scoring dyskinesia diaries were reduced approximately 50% after amantadine treatment compared with baseline or placebo phases. Similarly, dyskinesia assessments on the Unified Parkinson's Disease Rating Scale, part IV (items 32 and 33) also revealed significant improvement after treatment with amantadine. The magnitude of the L-dopa motor response to oral challenges was not different after amantadine or placebo treatment, and there was no significant reduction of daily off-time when patients received active treatment. These results confirm previous observations concerning the antidyskinetic potential of amantadine. **Key Words:** Amantadine—Dyskinesias—Parkinson's disease.

Although levodopa continues to be the gold standard of symptomatic efficacy in the drug treatment of Parkinson's disease (PD), it also induces potentially disabling drug-induced dyskinesias in the long term. Incidence figures of levodopa-induced dyskinesias vary between 20% and more than 80% after 5 to 6 years of treatment in various series[1] and seem to be particularly high in patients with early-onset PD.[2] In many instances, levodopa dose reduction and cotreatment with dopamine agonists is associated with sufficient reductions in dyskinesia intensity. In addition, strategies of continuous dopaminergic stimulation using subcutaneous apomorphine infusions[3,4] or continuous duodenal levodopa infusions[5,6] have also been shown to significantly ameliorate preexisting levodopa-induced dyskinesias in a certain proportion of patients. Also, much of the clinical impact of deep brain surgery in advanced PD is related to the potential of unilateral posteroventral pallidotomy[7,8] and deep brain stimulation of the globus pallidus internus[9,10] or nucleus subthalamicus[11–13] to significantly reduce levodopa-related dyskinesias. However, such procedures are still of limited accessibility, costly, and invasive so that the search for new antidyskinetic drugs in advanced PD is ongoing.

Recent experimental evidence has suggested a pathogenetic role of striatal N-methyl-D-aspartate (NMDA) receptor changes in the production of levodopa-induced dyskinesias. Amantadine, a noncompetitive NMDA receptor antagonist,[14–16] was indeed shown to possess antidyskinetic potential in MPTP-treated monkeys.[17] Rajput et al., in an open retrospective study,[18] claimed antidyskinetic effects of amantadine treatment in patients with PD with levodopa-induced dyskinesias, and this was substantiated in a double-blind, placebo-controlled trial by Verhagen Metman and colleagues.[19]

The present study was performed to confirm the efficacy of amantadine on levodopa-induced dyskinesias in another controlled double-blind, cross-over trial.

PATIENTS AND METHODS

Patients

Eleven patients (7 female and 4 male) with advanced PD complicated by motor fluctuations and L-dopa-induced dyskinesias gave their informed consent to participate in this 5-week study, which had been approved by the local ethics committee. Patients with dementia as

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well as renal, hepatic, or cardiac failure were excluded. The clinical characteristics of the study population are shown in Table 1. All but one patient experienced moderate to severe choreatic peak-dose dyskinesias; one patient had mixed dystonic and choreatic biphasic dyskinesias.

Methods

The study was designed as a double-blind, cross-over trial with two treatment periods of 2 weeks each separated by a 1-week wash-out interval. All antiparkinsonian medication was kept stable 4 weeks before and during the trial. Patients received identical-appearing tablets containing amantadine-sulphate or placebo. Amantadine-sulphate was titrated to 100 mg three times per day over 3 days with daily 100 mg increments.

Subjective dyskinesia intensity as well as daily "on"- and "off"-times were recorded by self-scoring "on"-/"off"-diaries over the last 3 days of each 2-week treatment period. Diary assessments of dyskinesia severity were performed on an hourly basis using a visual analog scale with either "no dyskinesias" or "maximally severe dyskinesias" as the end points (Fig. 1). This mode of daily dyskinesia recording allowed for estimations of the cumulative dyskinesia burden (intensity and duration) during the waking day. Cumulative dyskinesia scores were calculated by adding the cm-values from hourly visual analog scales and, together with cumulative daily off-time, were expressed as the mean of 3 consecutive days of recording.

In addition, oral levodopa challenges were performed before the first and on the last day of each treatment period. Antiparkinsonian medication was withheld overnight (12 hours), and on the following morning (8 AM) patients were challenged with 100/25 or 200/50 mg of water-soluble L-dopa/benserazide (Madopar LT®) orally depending on their regularly scheduled L-dopa morning dose. Dyskinesias were scored at baseline and every 20 minutes post-challenge using the Marconi dyskinesia rating scale.[20] Dyskinesias affecting the extremities, trunk, and neck were scored on a scale from 0 to 4 both at rest and during left and right finger-tapping activation (maximum score of 72). During the live dyskinesia rating, patients were videotaped and subsequently scored in an identical fashion by a second neurologist blind to the study procedure. For data analysis, scores were averaged using four time points from the beginning of the on state.

Finally dyskinesias were also assessed using part IV of the Unified Parkinson's Disease Rating Scale (UPDRS; items 32 and 33), as were activities of daily living scores (ADL scores) in the off-state using UPDRS part II. Parkinsonian symptoms were scored in defined-off and in best-on according to the UPDRS part III.[21]

Statistics

All statistical analysis were performed using the nonparametric Wilcoxon signed rank test. For statistical analysis, baseline scores for dyskinesias, UPDRS II in the "off" state, UPDRS III in the "on" and "off" state, UPDRS IV (items 32 and 33) were compared with the posttreatment/post-placebo scores. Daily off-time and cumulative dyskinesia scores observed in diary data were compared following amantadine versus placebo treatment period.

RESULTS

Ten of 11 patients completed the study; one patient was withdrawn while receiving placebo because of adverse events (dizziness). One of the 10 patients who finished the study experienced reversible edema of both feet during active amantadine treatment.

TABLE 1. *Patient characteristics*

Patient no.	Sex	Age (yrs)	Disease duration (yrs)	H & Y stage		Daily L-dopa dose (mg)	Dyskinesia duration (yrs)	Other PD medication
				On	Off			
1	F	75	14	3	4	600	7	Trihexyphenidyl
2	F	62	20	3	4	500	12	Bromocriptine, Entacapone
3	M	54	7	1	3	650	1.5	Pergolide
4	M	67	28	3	4	600	17	Bromocriptine
5	M	68	20	3	5	1300	13	Pergolide, Tolcapone, Apomorphine
6	F	65	16	3	4	1100	12	Bromocriptine, Tolcapone
7	F	52	9	1	3	800	3	Pergolide
8	M	58	22	2	3	600	14	Pergolide
9	M	62	12	3	5	1000	9	Pergolide, Tolcapone
10	F	57	12	3	5	950	9	Pergolide, Tolcapone
11	F	78	18	3	5	450	12	Pergolide
Mean ± SD		63.5 ± 8.2	10.1 ± 5.1	2.8 ± 1.2	3.8 ± 0.9	777 ± 274	10.1 ± 5.1	
Range		54–78	7–28	1–3	3–5	450–1300	3–17	

H & Y stage, Hoehn & Yahr stage; PD, Parkinson's disease; SD, standard deviation.

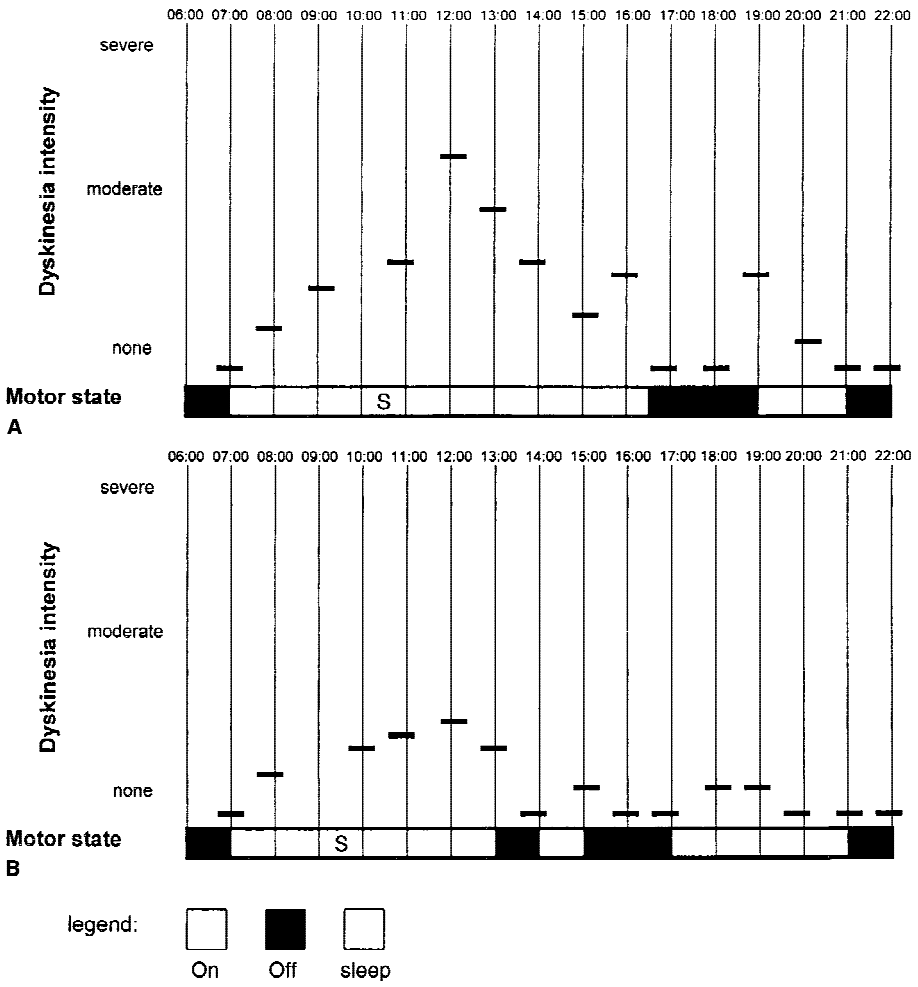

FIG. 1. (**A** and **B**) Patient diary showing a visual analog scale (vertical lines) for the hourly self-scoring of dyskinesia severity as well as daily on- and off-time (horizontal boxes). **A** represents a diary example following the placebo treatment period and **B** shows the completed diary of the same patient (patient no. 7) after the amantadine treatment period.

Dyskinesia severity following oral L-dopa challenges was significantly reduced by 52% after oral amantadine treatment (baseline score 14.5 ± 9.4 vs post-treatment score 7.0 ± 8.2; $p < 0.05$), whereas there was no change after placebo treatment (baseline score 16.6 ± 11.4 vs post-placebo score 15.5 ± 12.1; $p > 0.05$; Fig. 2). The corresponding scores were almost identical when analyzing the data set from the second blind video rater (base-

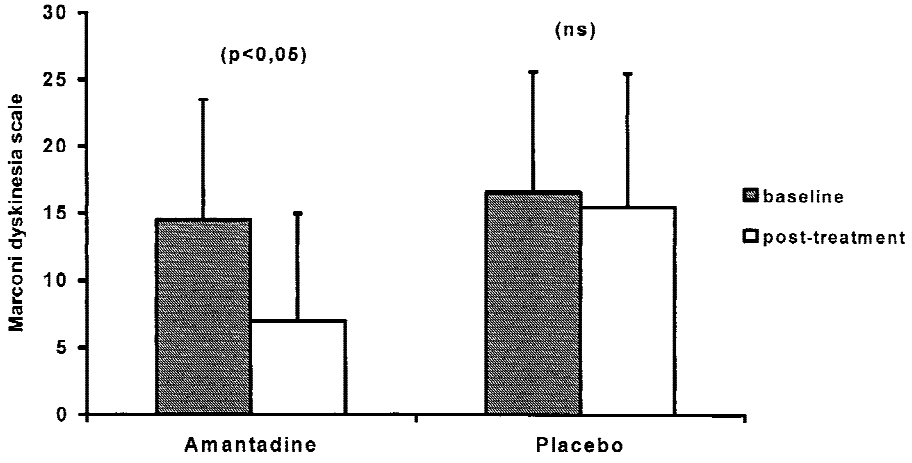

FIG. 2. Dyskinesia scores (Marconi scale) after oral L-dopa challenge tests.

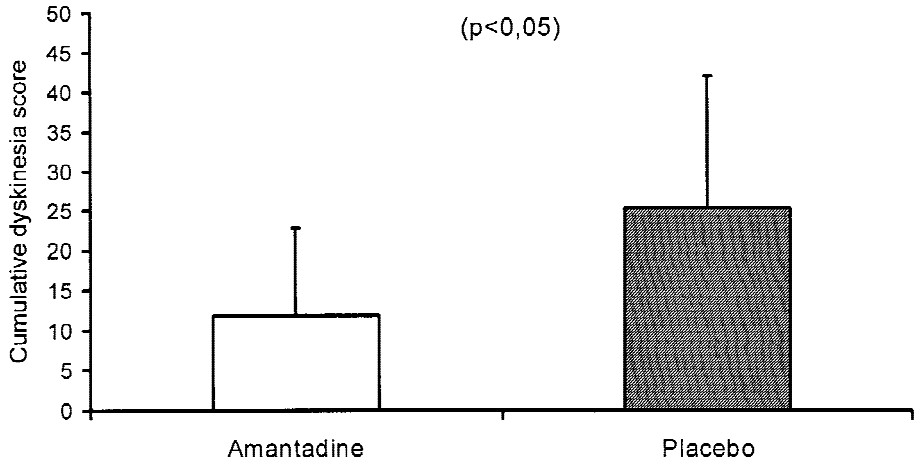

FIG. 3. Cumulative dyskinesia scores from self-scoring diaries after amantadine (open bars) or placebo (shaded bars) treatment periods showing significant reduction ($p < 0.05$) after amantadine compared with placebo.

line score 19.3 ± 13.7 vs post-treatment score 9.1 ± 9.1; $p < 0.05$).

Analysis of the diary data also showed a significant reduction in the cumulative dyskinesia score by 53% (post-amantadine treatment period 11.9 ± 11.4 vs post-placebo period 25.6 ± 16.7; $p < 0.05$; Figs. 1 and 3). Dyskinesia-duration as well as dyskinesia-disability, as measured by the UPDRS part IV items 32 and 33, were significantly reduced with amantadine (baseline score 3.4 ± 0.3 vs post-treatment score 1.7 ± 0.5; $p < 0.05$).

The magnitude of the L-dopa response, as measured by percent reduction of the UPDRS part III, was unchanged by amantadine or placebo treatment compared with baseline (Fig. 4). Daily off-time tended to be reduced in the amantadine treatment period, but the difference was not statistically significant (post-amantadine treatment period 3.11 ± 2.7 hrs vs post-placebo period 4.4 ± 3.1 hrs; $p > 0.05$).

There were no differences between patients receiving amantadine in the first or second treatment period.

DISCUSSION

Oral amantadine add-on therapy led to a statistically significant reduction of the severity of L-dopa-induced dyskinesias in this group of patients with advanced PD. This improvement was evident both following acute oral L-dopa challenge tests using an objective semiquantitative dyskinesia rating as well as in subjective dyskinesia assessments by the patients themselves using a modified diary chart. Similarly, positive results have recently been reported by Verhagen et al.[19]

These authors had used dyskinesia intensity during short levodopa infusions as the prime criterion for efficacy, supplemented by scores on items 32 and 33 of UPDRS part IV to assess dyskinetic intensity plus duration during oral amantadine treatment. In this study, assessment methods of dyskinesia closer reflected the everyday clinical situation by rating dyskinesias following oral challenges with the patients' individual morning dose size, as well as by using self-scoring dyskinesia diaries. By measuring the cumulative dyskinesia score from hourly data points on a visual analog scale, a mea-

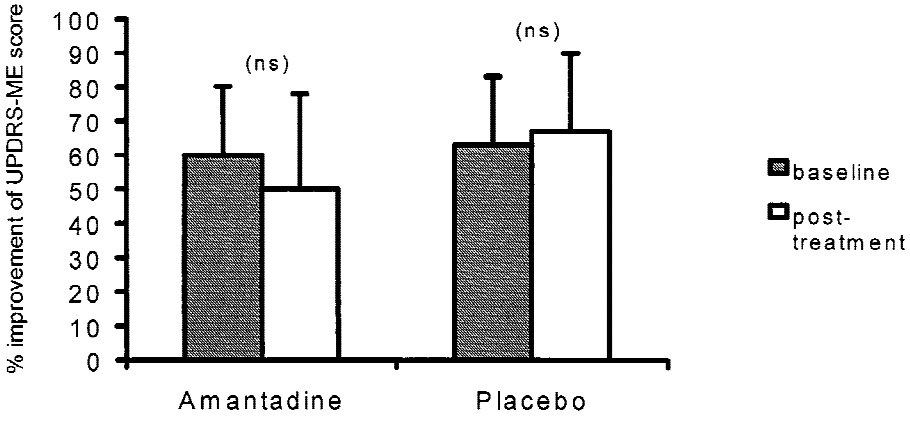

FIG. 4. L-Dopa motor response after oral single dose challenge (maximum percent reduction of UPDRS III scores).

sure of dyskinesia intensity plus duration was obtained. There was a remarkable consistency among the various dyskinesia assessment used: live rating, video rating by a second neurologist blind to the study procedure, and diary data all showed reductions in the order of 50%.

While Verhagen Metman et al.[19] observed a significant reduction in severity and duration of daily off-time, the current study revealed only a trend toward a reduction of daily off-time without reaching statistical significance. This is also different from the results of another small study reporting beneficial amantadine effects on motor fluctuations.[22] The lack of additional antiparkinsonian benefit from amantadine observed in this study most likely reflects a ceiling effect in patients who were on individually optimal dopaminergic replacement regimens before entering the trial.

Mechanisms underlying the antidyskinetic potential of amantadine are not completely understood. Amantadine has been shown to act as a noncompetitive glutamatergic NMDA receptor antagonist,[14–16] and Chase and colleagues have produced evidence for a role of NMDA receptors on striatal medium spiny neurons in the pathogenesis of levodopa-induced motor complications.[23]

In addition, antagonists of glutamate receptors have been demonstrated to block the functional consequences of subthalamic overactivity when stereotactically injected into the internal globus pallidus (Gpi) of MPTP-treated monkeys.[24] The administration of NMDA antagonists like amantadine might therefore counteract dyskinesias by way of "pharmacologic pallidotomy."

Whichever mechanism might be responsible, there is considerable experimental evidence that NMDA receptor antagonists can be beneficial in levodopa-induced dyskinesias.[25–27] There is also growing clinical evidence obtained with other NMDA antagonistic drugs like dextromethorphane and dextrophane, leading to reduced severity of levodopa-induced dyskinesias in small pilot trials.[28] On the other hand, memantine, a NMDA receptor antagonist with higher affinity compared with amantadine, failed to reduce levodopa-induced dyskinesias in a recent small, double-blind trial.[29] Recently, another open-label pilot trial using riluzole again found significant reductions of dyskinesia intensity and discussed NMDA glutamate antagonism as a possible underlying mechanism of riluzole's antidyskinetic effect.[30]

These results, together with the observations made in this trial, support the antidyskinetic potential of NMDA antagonism as a possibility of modifying levodopa-induced dyskinesias through drugs acting outside the nigrostriatal dopamine projection. Other potential antidyskinetic drugs modulating basal ganglia output circuitry include opioid receptor antagonists, cannabinoid receptor agonist or antagonists, alpha-2-adrenergic receptor antagonists, and 5-HAT agonists.[31]

For the time being it appears highly warranted to give patients with levodopa-induced dyskinesias a trial of oral amantadine before resorting to more complex procedures like subcutaneous apomorphine infusions or ultimately deep brain surgery.

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