Amantadine for Levodopa-Induced Dyskinesias

A 1-Year Follow-up Study

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Background: In a recent acute study, amantadine was found to have antidyskinetic effect against levodopa-induced motor complications in patients with Parkinson disease. The longevity of this effect was not addressed but is of interest in light of the controversy in the literature regarding the duration of amantadine’s well-established antiparkinsonian action.

Objective: To determine the duration of the antidyskinetic effect of amantadine in advanced Parkinson disease.

Design: One year after completion of an acute, double-blind, placebo-controlled, crossover study, patients returned for re-evaluation of motor symptoms and dyskinesias using a nonrandomized, double-blind, placebo-controlled follow-up paradigm.

Setting: National Institutes of Health Clinical Center.

Patients: Seventeen of the original 18 patients with advanced Parkinson disease complicated by dyskinesias and motor fluctuations participated in this study; 1 was lost to follow-up. Thirteen of the 17 individuals had remained on amantadine therapy for the entire year.

Interventions: Ten days prior to the follow-up assessment, amantadine was replaced with identical capsules containing either amantadine or placebo.

Main Outcome Measures: Parkinsonian symptoms and dyskinesia severity were scored using standard rating scales, while subjects received steady-state intravenous levodopa infusions at the same rate as 1 year earlier.

Results: One year after initiation of amantadine cotherapy, its antidyskinetic effect was similar in magnitude (56% reduction in dyskinesia compared with 60% 1 year earlier). Motor complications occurring with the patients’ regular oral levodopa regimen also remained improved according to the Unified Parkinson’s Disease Rating Scale (UPDRS-IV).

Conclusion: The beneficial effects of amantadine on motor response complications are maintained for at least 1 year after treatment initiation.

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HYPERFUNCTION of N-methyl-D-aspartate (NMDA) receptors on striatal efferent neurons has been linked to the development of motor response complications in advanced Parkinson disease (PD). Support for this hypothesis derives not only from animal models of PD, but also from controlled studies of NMDA receptor antagonists in patients with PD.

We recently reported the beneficial effects of amantadine, which also possesses NMDA antagonistic properties, on levodopa-associated dyskinesias and motor fluctuations. In that double-blind, placebo-controlled, crossover study, amantadine acutely reduced dyskinesias by 60%, while motor fluctuations improved as well.

The duration of amantadine’s antiparkinsonian benefit is unclear. Some studies show a decline in efficacy after 30 days; others, a decline after 5 to 7 months; yet other studies show a long-lasting amelioratory effect. To evaluate the persistence of the newly recognized antidyskinetic effect of amantadine, we performed a 1-year follow-up study with the same group of patients that participated in our initial clinical trial.

All 17 patients completed the study; no adverse effects occurred. The intravenous levodopa infusions at steady state provided stable antiparkinson and dyskinetic conditions in all individuals as indicated by low coefficients of variation (0.103 and 0.379 for parkinson and dyskinesia scores, respectively).
PATIENTS AND METHODS

Seventeen of the 18 patients who enrolled in the initial crossover trial consented to participate in this long-term study; 1 was lost to follow-up. Thirteen of the 17 patients had been treated with amantadine for 1 year. Three patients had not been able to tolerate amantadine during the original trial and were never rechallenged. The remaining individual discontinued amantadine treatment after 6 months, when it became clear that stopping selegiline was sufficient to reduce his dyskinesia. The present trial thus involved 13 patients on long-term amantadine therapy and 4 patients taking no amantadine. Mean ± SEM time to follow-up was 12 ± 0.5 months. Average age was 61 ± 3 years; symptom duration, 14 ± 1.4 years; and levodopa treatment duration, 12 ± 1.3 years. An effort was made to keep antiparkinsonian medications constant over the 1-year period; 12 individuals were treated with the same antiparkinsonian regimen. Daily levodopa dose was decreased by 25% in 4 individuals. Three were switched to another dopamine agonist, and 1 started treatment with an agonist. One patient began tolcapone treatment, and 3 stopped taking selegiline.

Seven to 10 days prior to study, the 13 individuals taking amantadine discontinued this medication; all 17 patients were then given identical-appearing capsules prepared by the National Institutes of Health Pharmaceutical Development Service. They were told that these capsules contained either 100 mg of amantadine hydrochloride or placebo. Neither patients nor evaluators were aware of drug assignment. Evaluators were not involved in the clinical care of the patients at any time. Only a safety officer, not involved in outcome evaluations, knew the design of the study and assigned the active drug to the 13 individuals who had been treated with amantadine maintenance therapy and placebo to the 4 others. All received the same number of capsules they had received during the initial assessment 1 year earlier (1 capsule, 3 or 4 times a day). Although this was 1 capsule more than they had been receiving throughout the year for 9 of the patients, we felt it was necessary to compare assessments at the same dose level. This small dose increase was not associated with subjective changes in any patient. This single-arm design was chosen for several reasons: (1) a crossover trial after long-term amantadine therapy would have required a long washout period, which would have interrupted the continuous, long-term aspect of amantadine administration, possibly defeating the purpose of the study and contributing to patient discomfort; (2) withdrawal of amantadine after long-term use may exacerbate motor disability and even cause acute delirium13; (3) 3 of the 4 patients who had not been receiving amantadine had experienced adverse effects during the original study, and we elected not to reexpose them to this drug.

Motor assessments were carried out under identical (inpatient) conditions as in the original study. Briefly, oral levodopa/carbidopa and other antiparkinsonian medications were discontinued at 11 PM on the night prior to levodopa infusion. Starting at the same time as 1 year before (5 or 6 AM), patients received an intravenous levodopa infusion for 7 hours at the same individualized optimal rate as 1 year earlier (64 ± 5 mg/h). Carbidopa was coadministered orally. Patients received a 5-g low-protein breakfast, and lunch was withheld until testing was completed. During the last 2 hours of levodopa infusion, after steady-state conditions had been achieved, parkinsonian symptoms and choreiform dyskinesias were scored every 10 minutes by the same masked neurologist who had evaluated the patients 1 year earlier, using an abbreviated motor subscale of the Unified Parkinson’s Disease Rating Scale (UPDRS) (UPDRS-III, items 20, 22, 23, 26, 29, and 31, describing tremor, rigidity, finger taps, leg agility, gait, and body bradykinesia on a scale from 0-4) and Abnormal Involuntary Movement Scale rating involuntary movements in all extremities and trunk and face on a scale from 0 to 4 (maximum score of 64 for parkinsonism and 20 for dyskinesias).8

Dyskinesias were also videotaped during the live rating and scored by a second masked neurologist, also the same person who rated the video segments 1 year earlier, using the same scale as the live rater. To reduce intrarater variability over time, the video rater rescored dyskinesias recorded the previous year. Video segments were offered for evaluation in random order. Motor complications were further assessed with UPDRS-IV. Activities of daily living (ADLs) were assessed with UPDRS-II.

Plasma samples were taken 3 hours after amantadine or placebo ingestion on the day of testing. Amantadine levels were measured as before. Data are expressed as mean ± SEM. Statistical analysis was performed with Wilcoxon signed rank tests. Variability of dyskinesia and parkinson scores during levodopa infusion was estimated by the coefficient of variation. The intraclass correlation coefficient was used to measure interrater agreement.

THE AMANTADINE GROUP (n = 13)

The average amantadine dose was 362 ± 14 mg, and plasma amantadine levels averaged 9.7 ± 0.9 μmol. Dyskinesia scores during steady-state levodopa infusions were 56% lower than those measured during the placebo arm of the initial acute study (2.6 ± 0.3 vs 5.9 ± 0.9; P<.01) (Figure 1, left). Dyskinesia reduction was not associated with increased parkinsonism as parkinson scores were not significantly different from those obtained with placebo in the initial study (6 ± 1.1 vs 7.1 ± 1.6, respectively) (Figure 1, left).

Dyskinesia ratings from videotapes by a second masked rater indicated a 43% dyskinesia reduction compared with the placebo arm of the initial acute study (3.6 ± 0.6 vs 6.3 ± 0.8; P<.05). The intraclass correlation coefficient for “live” and “videotape” raters was 0.77 (excellent agreement beyond chance).

During the outpatient administration of oral levodopa and amantadine, the duration and severity of dyskinesias (UPDRS-IV, items 32 and 33) and the duration of daily “off” time (UPDRS-IV, item 39) were significantly better than with placebo in the initial study. The UPDRS-II scores tended to remain better as well, but this no longer reached statistical significance (Table).

PLACEBO GROUP (n = 4)

Dyskinesia scores in all 4 patients who received placebo tended to be higher (5.5 ± 1.3) than those during the pla-
cebo arm in the initial study (3.4 ± 0.6; \( P = .07 \)), while the antiparkinson scores were unchanged (9.2 ± 4.3 and 11.1 ± 3.7, respectively; \( P = .7 \)) (Figure 1, right).

**COMMENT**

The results of this follow-up study indicate that 1 year after initiation of amantadine therapy, the reduction in levodopa-induced motor response complications persists. Moreover, the magnitude of the effect is undiminished; for the 13 long-term amantadine users, average dyskinesia scores remained over 50% lower than with placebo 1 year earlier (Figure 1, left). Plasma amantadine concentrations after 1 year of therapy were unchanged from those in the initial acute study. Visual inspection of the data (Figure 2) reveals that all 13 patients had lower dyskinesia scores than those measured during the placebo arm of the initial study. Compared with the amantadine arm of the original study, only 2 patients had clearly higher dyskinesia scores; of the remaining 11 patients, 7 had slightly lower and 4 slightly higher scores at follow-up. In contrast, dyskinesia scores in all 4 patients who received placebo were higher in the current study than during the placebo arm of the initial trial (Figure 1, right). Although the number of patients in this placebo group was relatively small, and they were not randomly assigned to this treatment arm, their data illustrate that dyskinesia severity does not decrease spontaneously, but more likely increases over time. The outcome of the UPDRS-IV interview, based on the patients’ regular oral antiparkinson regimen, suggests that these findings can be extended to the clinical situation.

The duration of amantadine’s antiparkinson effect has been debated since its introduction into clinical practice. Assuming that antiparkinson and antidyskinetic effects are mediated by a similar pharmacological mechanism, the cur-
rent results support the notion that the antiparkinson effect of amantadine is not restricted to the first few months of therapy,9,10 but is longer lasting.11,12 Such a sustained effect is also suggested by the UPDRS-II scores, which, even though significance was lost, were still lower and at least not higher than with placebo during the initial study.

The present findings hold the promise that clinicians will have a pharmacological tool that may maintain its efficacy in the long-term treatment of levodopa-induced dyskinesias; furthermore, they lend credence to the strategy of submitting patients to an adequate trial of amantadine prior to considering surgical procedures for severe dyskinesias.

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