Citation: Clin Transl Sci (2019) 12, 586–590; doi:10.1111/cts.12684

BRIEF REPORT

Effect of Repeated Intravenous Amantadine Infusions in Patients with Parkinson's Disease: An Open-Label Pilot Study

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Amantadine is an antiviral drug available in oral and intravenous forms. Oral amantadine is used to treat the motor symptoms of early Parkinson's disease (PD) and to ameliorate dyskinesia in late-stage disease. However, the long-term influence of intravenous amantadine on motor symptoms and dyskinesias in PD has not been investigated. The aim of the present study was to examine the long-term effect of repeated boosts of intravenous amantadine in patients with PD with and without response fluctuations and dyskinesias. Twelve patients diagnosed with PD, six with levodopa intolerance or insufficient response to antiparkinson medications, and six with response fluctuations and dyskinesias, were treated with intravenous amantadine for 6 months: three sequential infusions over 3 days in the first month followed by five once-monthly infusions. Changes in motor function and involuntary movements were evaluated with the Unified Parkinson Disease Rating Scale (UPDRS) and Abnormal Involuntary Movement Scale (AIMS; dyskinesia group). A significant immediate improvement in motor scores was documented in both groups after amantadine infusion. However, the difference in mean UPDRS motor score from before the first infusion to after 6 months of treatment was not statistically significant. In patients with dyskinesias, there was a significant improvement in AIMS scores between the first and the last visits (6.3 ± 2.7 vs. 1.6 ± 1.3; $P = 0.014$). In conclusion, continuous treatment with intravenous amantadine can be useful in patients with PD for immediate relief of motor symptoms and in patients with dyskinesias for progressive reduction of involuntary movements.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Amantadine is effective drug in the treatment of Parkinson's disease (PD) that does not have a direct effect on the dopaminergic system. The oral formula is effective in reducing severity of dyskinesias and tremor for a long run. Intravenous amantadine was shown to have an immediate effect on dyskinesias.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The aim of the study was to evaluate the long-term effects of intravenous amantadine on patients with dyskinesias and patients who could not tolerate levodopa treatment.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This study showed long-term improvement in dyskinesia scores and stable immediate motor improvement in patients with and without dyskinesias that was preserved for at least 6 months from the beginning of treatment.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Long-term intravenous amantadine might be an effective treatment for ameliorating dyskinesias and improving motor symptoms of patients with PD.

Levodopa is still considered the gold standard treatment for most of the motor symptoms in Parkinson's disease (PD). However, a large number of patients cannot be managed effectively by levodopa because of an insufficient response or adverse effects, mainly vomiting, vertigo, and orthostatic hypotension.[1,2] Moreover, almost 70% of patients who do respond to levodopa will acquire troublesome dyskinesias and response fluctuations within 5 years of treatment.[3] One strategy to overcome levodopa-induced dyskinesias is to reduce the dopaminergic medications at the expense of increased "off" periods. However, most patients prefer remaining in the "on" period with dyskinesias to becoming akinetic in the "off" period.[4,5]

One of the core pathogenetic mechanisms underlying dyskinesias in PD is over-reactivity of the excitatory striatal output pathway due to an excessive glutaminergic influence of the corticostriatal projections to the striatum.[6] Amantadine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist with dopaminergic properties. It is unique in its dual mode of action: it improves motor functions[7,8] while ameliorating

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Received: April 9, 2019; accepted: July 8, 2019. doi:10.1111/cts.12684

dyskinesias. This is probably achieved by its reduction of the *N*-methyl-D-aspartate sensitivity of the striatal medium spiny neurons to glutaminergic input[9] and prevention of gamma-Aminobutyric acid (GABA) release at the substantia nigra.[10] Clinical trials showed a short-term antidyskinetic effect of amantadine in patients with advanced PD.[11–14]

The aim of the present study was to investigate the long-term effect of repeated intravenous infusions of amantadine in patients with PD with and without response fluctuations and dyskinesias. An open-label design was used, with inclusion of patients with moderate disease who could not tolerate or had insufficient response to levodopa therapy and patients with advanced disease and levodopa-induced dyskinesias.

METHODS

Patients

Patients with PD were recruited from the Movement Disorder Unit of Rabin Medical Center. The study was approved by the local institutional ethics committee and the Israel Ministry of Health and was registered in the clinical trial registry of the National Institute of Health (NCT01190553). All patients had idiopathic PD according to the criteria of the United Kingdom Brain Bank with unilateral bradykinesia and/or rigidity and tremor. All patients signed an informed consent form. Patients underwent kidney function tests and electrocardiograms before enrolling. Those with abnormal kidney tests, cardiac arrhythmias, and known sensitivity to amantadine were excluded.

Experimental protocol

Patients arrived in the morning, before starting any antiparkinsonian treatment. A standard regimen of intravenous amantadine 200 mg in a 500 cc saline solution was administered over 3 hours. All patients were tested for response to treatment under the same conditions, in the same chair, by the same trained neurologist (A.K.). A total of six dosing visits were conducted. In the first visit, patients received daily amantadine infusions for three sequential days. This was followed by five once-monthly visits in which patients received a single infusion of the same dose (200 mg in 500 cc saline). During the study, all patients were treated with oral amantadine between visits. Patients already being treated with oral amantadine did not take the drug on days of amantadine infusion.

To reduce the influence of dopamine-containing drugs, oral dopaminergic medications were administered after motor symptoms were evaluated. Disease severity was assessed at each visit before and after treatment using the motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS).[15] The severity of levodopa-induced dyskinesias was assessed with the Abnormal Involuntary Movement Scale (AIMS),[16] at each visit before amantadine infusion (from 8 AM to 9 AM) and 30 minutes after its completion (from 11 AM to 12 PM).

Statistical analysis

Statistical analysis was performed using the SPSS version 19 (Chicago, IL). Demographic data were analyzed by *t*-test (age) or Wilcoxon test (motor scores). Paired *t*-test for independent samples was used to compare motor scores and dyskinesia scores before and after infusion of amantadine at each visit and between the first and final visits.

RESULTS

Twelve patients were enrolled in the study, six with dyskinesias, and six without dyskinesias and motor fluctuations. In the group with dyskinesias, mean age was 74.0 ± 3.3 years and mean disease duration 13.3 ± 4.9 years. The initial mean UPDRS motor score was 35.7 ± 12.4 (range 21–57), and the initial mean AIMS score was 6.33 ± 2.7 (range 2–10). In the group without dyskinesias, mean age was 68.3 ± 7.6 years, mean disease duration was 5.7 ± 2.5 years, and the initial mean UPDRS motor score was 31.5 ± 11.9 (range 13–48).

Four of the six patients without dyskinesias could not tolerate levodopa, and the other two had minor response to the drug in low doses but could not tolerate any increase of dosage. All patients with dyskinesias were receiving levodopa treatment, of whom four had been treated with oral amantadine for at least 1 year prior to the study. Two patients without dyskinesias were receiving treatment with levodopa and one was also receiving oral amantadine. The drug regimen in the patients in both groups being treated with oral amantadine had not been changed for at least 6 months before their entry to the study.

Five patients with dyskinesias completed all study visits; the remaining patient dropped out after four visits owing to a hip fracture following a fall. Of the patients without dyskinesias, three completed all study visits and three dropped out because of a lack of response: two patients after three visits and one patient after four visits.

Analysis of the response to repeated intravenous amantadine treatment showed that in the patients with moderate disease without dyskinesias (**Table 1**), amantadine infusion had a significant acute effect on the UPDRS motor score after visits 1, 2, 3, and 5, with a trend for improvement after visits 4 and 6. The change in mean motor score from onset of treatment (before the first infusion; 31.5 ± 11.9) to after 6 months of treatment (following the last infusion; 25.3 ± 16.7) was not statistically significant (P = 0.3). In the advanced-disease group with dyskinesias (**Table 2**), there was a trend for improvement of the UPDRS score from before to after each visit. A significant difference in mean UPDRS motor score was recorded at all visits except the first. The change in mean UPDRS motor score from onset of treatment (35.7 ± 12.4) to after 6 months of treatment (24.8 ± 11.6) was not statistically significant (P = 0.6). An acute improvement in mean AIMS dyskinesia score was noted after visit 1 (from 6.3 ± 2.7 before the visit to 2.17 ± 2 after; P = 0.001) and visit 2 (from 4.3 ± 1.5 to 1.8 ± 2.2; P = 0.02). In addition, there was a trend for improvement of the AIMS score after visit 6 (from 3.8 ± 2.2 to 1.6 ± 1.3; P = 0.06). Comparison of the AIMS dyskinesia scores between the first visit (6.3 ± 2.7) and the last (1.6 ± 1.3) yielded a statistically significant difference (P = 0.014).

There were no major amantadine-related side effects during the study. Two serious adverse events unrelated to

Table 1 Changes in UPDRS scores for individual visits in patients without dyskinesias

		UPDRS motor score before and after amantadine infusion											
		Visit 1 (n = 6)		Visit 2 (n = 6)		Visit 3 (n = 6)		Visit 4 (n = 4)		Visit 5 (n = 3)		Visit 6 (n = 3)	
Pt. no./sex	Continuous treatment	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1/F	Levodopa, ropinorole	32	16	23	14	34	28	32	25	35	25	27	20
2/M	Levodopa, oral amantadine	40	39	35	27	48	36	47	45	39	33	52	44
3/M	Rasagiline	29	11	35	21	27	21	30	15	23	11	28	12
4/M		48	27	40	32	41	30	49	30	—	—	—	—
5/F		13	8	25	13	30	14	—	—	—	—	—	—
6/F	Pramipexol, ropinorole, rasagiline	27	22	21	13	29	17	—	—	—	—	—	—
Mean score		31.5 ± 11.9	20.5 ± 11.4	29.8 ± 7.8	20.0 ± 8.0	34.8 ± 8.1	24.3 ± 8.4	39.5 ± 9.9	28.7 ± 12.5	32.3 ± 8.3	23 ± 11.1	35.6 ± 14.41	25.3 ± 16.7
P value[a]		0.023		0.0001		0.001		0.068		0.034		0.068	

UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Change from before to after treatment.

Table 2 Changes in UPDRS scores for individual visits in patients with dyskinesias

		UPDRS motor score before and after amantadine infusion											
		Visit 1 (n = 6)		Visit 2 (n = 6)		Visit 3 (n = 6)		Visit 4 (n = 6)		Visit 5 (n = 5)		Visit 6 (n = 5)	
Pt. no./sex	Continuous treatment	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1/M	Levodopa, pramipexole	35	22	33	25	34	35	39	26	39	27	41	24
2/M	Levodopa, amantadine, ropinorole	21	10	22	14	30	28	18	16	24	17	28	15
3/M	Levodopa, amantadine, rasagiline COMT inhibitor	37	24	33	22	32	28	31	23	37	31	39	31
4/F	Levodopa	57	44	57	46	57	53	53	43	50	45	53	41
5/M	Levodopa, amantadine	26	10	25	8	21	11	21	6	23	11	21	13
6/M	Levodopa, amantadine, ropinorole	38	52	51	49	38	35	46	37	—	—	—	—
Mean score		35.7 ± 12.5	27.0 ± 17.5	36.8 ± 14.1	27.3 ± 17	35.3 ± 12.0	30.0 ± 14.8	36.3 ± 11.9	25.2 ± 13.5	34.6 ± 11.3	26.2 ± 13.2	36.4 ± 12.4	24.8 ± 11.6
P value[a]		0.117		0.005		0.042		0.0001		0.005		0.002	

UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Change from before to after treatment.

amantadine were recorded (fall with right hip fracture and elective total knee replacement).

DISCUSSION

The rationale for continuous repeated intravenous amantadine treatment in patients with PD is based on findings of an improvement in motor function and amelioration of dyskinesias in long-term studies of oral amantadine and short-term studies of intravenous amantadine. The present pilot study sought to determine the effectiveness of boosts of intravenous amantadine.

Our results indicate that repeated intravenous infusions over 6 months significantly reduce levodopa-induced dyskinesias, with no loss of the benefit of levodopa. The drop in dyskinesia scores ranged from 25% to 33% by the end of the trial. However, there was no continuous reduction in dyskinesia scores and no long-term improvement of parkinsonian symptoms. A trend for improvement of the UPDRS motor scores was noted between visits, probably owing to the weak dopaminergic effect of amantadine, which could not surpass the ceiling effect of levodopa.

These results are in agreement with previous studies of amantadine in PD. These studies focused mainly on long-term oral treatment or short-term intravenous infusions. The first double-blind randomized study of oral amantadine, conducted in 14 patients, documented significant improvement of dyskinesias after 3 weeks.[17] Since then, others have shown both acute and long-term antidyskinetic effects in > 50% of patients with advanced disease. As in the former study, oral amantadine was used.[18,19] In 17 patients who were re-examined after 1 year of treatment with oral amantadine, the beneficial antidyskinetic effect remained nearly to the magnitude of the acute effect.[20] Acute intravenous amantadine also reduced dyskinesias by nearly 50%[13]; this effect lasted for at least 5 hours.

In our study, plasma levels of amantadine were not evaluated, but we assumed that peak levels are gained rapidly following intravenous administration and that they remain high for several days, adding to the levels achieved by the regular oral treatment. One reason for this could point to the different pharmacokinetics of oral and intravenous amantadine, as shown in an animal study by Siao *et al*.[21] In the patients with moderate disease without dyskinesias, an acute improvement in motor symptoms was noted immediately after amantadine infusion. However, it did not last for many days, as indicated by the lack of improvement in UPDRS motor scores compared with the previous visit. Indeed, not only there was no long-term improvement in UPDRS scores after 6 months of treatment, the final mean score was only slightly and nonsignificantly higher than the initial score, most probably as a consequence of the rapid disease progression in two of the patients.

Oral amantadine is commonly used in the treatment of early PD, especially in patients reluctant to initiate treatment with levodopa. Data on the duration of its beneficial effect are limited. A few nonrandomized studies showed significant improvement in motor scores,[22,23] but thus far, studies of the long-term effect of intravenous amantadine in non-levodopa-treated patients with early disease are lacking. Parenteral amantadine is commonly used in patients undergoing major abdominal surgeries who are unable to consume medications.[24,25] Another advantage of intravenous amantadine is its potential to acutely improve freezing symptoms.[14,23] Therefore, in our study, the patients with dyskinesias apparently reached their steady state, which would explain the lack of significant change in UPDRS scores after the third visit.

This study was limited by its open-label design and the large variability in patient background characteristics. Furthermore, the sample was too small for us to draw conclusions regarding the use of this mode of treatment in patients who are unable to tolerate levodopa. Another drawback of the study is that 1 of the 6 patients without dyskinesias and 4 of 6 patients with dyskinesias had been treated with oral amantadine before enrollment to the study. This fact may have had a possible influence on the reaction to intravenous amantadine infusion. The small number of amantadine-naïve patients makes it difficult to fully evaluate the effect of intravenous infusions. The small sample size may also explain the lack of statistically significant results in UPDRS and dyskinesia scores.

In conclusion, our preliminary results may point to a beneficial effect of intravenous amantadine in patients who are unresponsive to conventional antiparkinsonian medications and for treatment of response fluctuations and dyskinesias. Further studies with larger samples are warranted to investigate the long-term effects of intravenous amantadine on dopaminergic and nondopaminergic (freezing gait and falls) symptoms in PD.

Funding. No funding was received for this work.

Conflicts of Interest. I.S. serves on the editorial board of the Journal of Neurological Sciences, Journal of NeuroVirology, and Medicine Neurology (Hebrew). He is a consultant and member of the Data Safety Monitoring Board for Actelion and Genentech/Roche. He received honoraria from Teva Pharmaceutical Industries Ltd. All other authors declared no competing interests for this work.

Author Contributions. A.K., I.S., and R.D. wrote the manuscript. I.S., T.T., and R.D. designed the research. A.K. and R.D. performed the research. T.T. analyzed the data.

1. Horstink, M.W. Problems of levodopa treatment. *Clin. Neurol. Neurosurg.* **86**, 196–206 (1984).
2. Vajda, F.J., Donnan, G.A. & Bladin, P.F. Patterns of response to levodopa in Parkinson's disease. *Clin. Exp. Neurol.* **15**, 299–306 (1978).
3. Hauser, R.A., McDermott, M.P. & Messing, S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. *Arch. Neurol.* **63**, 1756–1760 (2006).
4. Schrag, A. & Quinn, N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain* **123**, 2297–2305 (2000).
5. Khlebtovsky, A. *et al.* Patient and caregiver perceptions of the social impact of advanced Parkinson's disease and dyskinesias. *J. Neural Transm.* **119**, 1367–1371 (2012).
6. Fabbrini, G., Brotchie, J.M., Grandas, F., Nomoto, M. & Goetz, C.G. Levodopa-induced dyskinesias. *Mov. Disord.* **22**, 1379–1389 (2007).
7. Dallos, V., Heathfield, K., Stone, P. & Allen, F.A. Use of amantadine in Parkinson's disease. Results of double blind trial. *Br. Med. J.* **4**, 24–26 (1970).
8. Butzer, J.F., Silver, D.E. & Sahs, A.L. Amantadine in Parkinson's disease. A double-blind, placebo-controlled, crossover study with long-term follow-up. *Neurology* **25**, 603–606 (1975).

9. Metman, L.V., Konitsiotis, S. & Chase, T.N. Pathophysiology of motor response complications in Parkinson's disease: hypotheses on the why, where, and what. *Mov. Disord.* **15**, 3–8 (2000).
10. Bido, S., Marti, M. & Morari, M. Amantadine attenuates levodopa-induced dyskinesia in mice and rats preventing the accompanying rise in nigral GABA levels. *J. Neurochem.* **118**, 1043–1055 (2011).
11. Snow, B.J., MacDonald, L., Mcauley, D. & Wallis, W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. *Clin. Neuropharmacol.* **23**, 82–85 (2000).
12. Thomas, A., Iacono, D., Luciano, A.L., Armellino, K., Di Iorio, A. & Onofrj, M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **75**, 141–143 (2005).
13. Del Dotto, P. *et al.* Intravenous amantadine improves levadopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov. Disord.* **16**, 515–520 (2001).
14. Kim, Y.E., Yun, J.Y. & Jeon, B.S. Effect of intravenous amantadine on dopaminergic-drug-resistant freezing of gait. *Parkinsonism Relat. Disord.* **17**, 491–492 (2011).
15. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov. Disord.* **18**, 738–750 (2003).
16. Guy, W. Abnormal Involuntary Movement Scale. In ECDEU Assessment Manual for Psychopharmacology. 534–537 (US Government Printing Office, Washington, DC, 1976).
17. Metman, L.V., Del Dotto, P., van den Munckhof, P., Fang, J., Mouradian, M.M. & Chase, T.N. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology* **50**, 1323–1326 (1998).
18. Luginger, E., Wenning, G.K., Bösch, S. & Poewe, W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov. Disord.* **15**, 873–878 (2000).
19. Wolf, E. *et al.* Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. *Mov. Disord.* **25**, 1357–1363 (2010).
20. Metman, L.V., Del Dotto, P., LePoole, K., Konitsiotis, S., Fang, J. & Chase, T.N. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch. Neurol.* **56**, 1383–1386 (1999).
21. Siao, K.T., Pypendop, B.H., Stanley, S.D. & Ilki, J.E. Pharmacokinetics of amantadine in cats. *J. Vet. Pharmacol. Ther.* **34**, 599–604 (2011).
22. Schwab, R.S., England, A.C. Jr, Poskanzer, D.C. & Young, R.R. Amantadine in the treatment of Parkinson's disease. *JAMA* **208**, 1168–1170 (1969).
23. Parkes, J.D. *et al.* Treatment of Parkinson's disease with amantadine and levodopa. A one-year study. *Lancet* **1**, 1083–1086 (1971).
24. Raz, A., Lev, N., Orbach-Zinger, S. & Djaldetti, R. Safety of perioperative treatment with intravenous amantadine in patients with Parkinson's disease. *J. Clin. Neuropharm.* **36**, 166–169 (2013).
25. Kim, Y.E., Kim, H.J., Yun, J.Y. & Jeon, B.S. Intravenous amantadine is safe and effective for the perioperative management of patients with Parkinson's disease. *J. Neurol.* **258**, 2274–2275 (2011).