

Repeated Intravenous Amantadine Infusions in Advanced Parkinsonism: Experience of a Large Movement Disorder Center

Meir Kestenbaum MD^{1,4}, Muneer Abu Snineh MD², Tamar Nussbaum MD³, Avi Gadoth MD^{3,4}, Alina Rosenberg⁴, Avigail Hindi³, Jennifer Zitser MD³, Avner Thaler MD PHD^{3,4}, Nir Giladi MD^{3,4,5} and Tanya Gurevich MD^{3,4,5}

¹Department of Neurology, Meir Medical Center, Kfar Saba, Israel

²Department of Neurology, Hadassah Medical Center, Jerusalem, Israel

³Department of Neurology, Tel Aviv Medical Center, Tel Aviv, Israel

⁴Sackler Faculty of Medicine, and ⁵Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** The effect of repeated intravenous amantadine (IVAM) in advanced Parkinsonism has not been studied in depth.

Objectives: To report the experience of our medical center with repeated IVAM infusions in patients with advanced Parkinsonism.

Methods: Thirty patients with advanced Parkinsonism of various etiologies were enrolled in an open-label retrospective study. All patients were treated with IVAM infusions in a neurological daycare center. Treatment was initiated with a loading dose of 200/400 mg per day for 5 days followed by a once-daily maintenance dose of 200/400 mg every 1 to 3 weeks. Patients and their caregivers participated in a structured interview and independently completed a clinical global impression of changes scale questionnaire on various motor and non-motor symptoms.

Results: Patient mean age was 73.3 ± 9.7 years, average disease duration was 6.2 ± 5.7 years, and mean Hoehn and Yahr score was 3.2 ± 0.84 . Mean duration of the IVAM treatment was 15.1 ± 11.6 months. An improvement in general function was reported by 91% of the patients and 89% of the caregivers. Most of the patients reported improvement in tremor and rigidity, as well as in gait stability, freezing of gait, and reduced falls. The treatment was safe with few side effects.

Conclusions: Our data suggest that repeated IVAM infusions could be an effective treatment against various motor symptoms and for improvement of mobility in patients with advanced Parkinsonism. Further randomized clinical trials with a larger sample size using objective measures are warranted to validate our results.

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KEY WORDS: intravenous amantadine (IVAM), Parkinson's disease (PD), Parkinsonism

Amantadine, an anti-glutamatergic agent with dopaminergic and anticholinergic properties, was first reported as early as 1969 to benefit rest tremor, rigidity, and akinesia of Parkinson's disease (PD) [1]. Since then, several clinical trials have investigated the efficacy of oral amantadine in PD, and their results have shown positive effects on motor symptoms [2], including gait [3]. Amantadine has been classified as being likely efficacious and possibly useful in symptomatic monotherapy and adjunct therapy, but with insufficient evidence and investigational validation for the treatment of motor fluctuations [4]. However, amantadine has been defined as being efficacious and clinically useful in the treatment of dyskinesia based on the findings of recent high-quality studies [5,6].

The duration of the benefit of amantadine in treating PD patients is not clear, with some studies suggesting that the benefit will be for no more than 4–8 weeks [1], while most studies show that patients maintain some long-term benefit [7]. The drug is generally well tolerated, with mainly mild side effects that include dry mouth, dizziness, leg edema, livedo reticularis, psychosis, and confusion [8]. Amantadine was shown to be capable of alleviating the signs of PD, as well as other Parkinsonian syndromes, by means of extrastriatal effects on the basal ganglia as an antagonist of glutamate N-methyl-D-aspartate receptors [9,10].

A number of clinical trials have assessed the effect of amantadine in treating Parkinson-plus syndromes, among them multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Some studies reported improvement in motor symptoms with amantadine treatment [11], and others reported improvement in ataxia with intravenous amantadine (IVAM) in an open-label trial on MSA patients [12]. The only placebo-controlled study that was conducted failed to provide any clinically significant motor benefit in patients with MSA [13].

Although IVAM followed by oral amantadine has been used in clinical practice, mostly in Europe, with good motor benefit

in advanced PD [14], only a few trials have investigated the effect of IVAM infusions for PD, and there are no reported data comparing the efficacy of oral amantadine and IVAM. One prospective open-label study on 30 PD patients [15] suggested that IVAM for 14 days is effective for both motor and cognitive functions, while another study showed that IVAM improved performance of complex but not simple motor tasks in 31 PD patients [16]. Two small open-label trials reported an improvement in both motor fluctuations and dyskinesias in PD patients treated with IVAM [14,17]. The results of the effect of IVAM infusions for freezing of gait were inconsistent (where is the conflict?). Two randomized, double blind, placebo-controlled trials failed to show any benefit of IVAM for freezing of gait in PD patients [18,19].

The effect of amantadine on overall quality of life for someone presenting with Parkinsonism has not been investigated in depth. There is no accepted protocol for the use of IVAM in the treatment of PD and Parkinsonism. Considering the paucity of published clinical data on IVAM treatment in Parkinsonism, we reported our experience with repeated IVAM in patients with advanced Parkinsonism.

PATIENTS AND METHODS

STUDY PARTICIPANTS AND DIAGNOSES

This study comprised 30 consecutive patients with advanced Parkinsonism of multiple etiologies (PD, PSP, MSA, vascular Parkinsonism, Parkinsonism not specific, and diffuse Lewy body disease). A movement disorders specialist working at a neurological daycare service at Tel Aviv Sourasky Medical Center referred the patients for treatment with IVAM due to significant disability. The study began in January 2013. The frequency and dose of IVAM was given to the patients according to the clinical judgement of a movement disorder specialist. Patient clinical data were collected and analyzed. All participants provided written informed consent prior to study participation. The study was approved by the Sourasky Tel Aviv Medical Center institutional review board.

BASELINE EVALUATION AND OUTCOME MEASURES

The enrolled patients were treated with IVAM with the aim of improving their clinical symptoms of advanced Parkinsonism. The patients' blood count and chemistry results prior to initiating the first treatment and annually thereafter were reviewed. The QT interval was measured, and an ophthalmological exam was performed to rule out corneal edema. Treatment was initiated by a loading dose of 200/400 mg per day for 5 days followed by a maintenance dose of 200/400 mg once every 1 to 3 weeks. The preparation used was amantadine sulfate 200 mg/500 ml (Merz Pharma GmbH & Co. KgaA, Frankfurt, Germany). Cross-sectional assessments were performed during the study period to patients who received IVAM at least

6 times (one 5-day course and once at an additional visit). Patients and their caregivers participated in a structured interview and independently completed a clinical global impression of changes scale (CGICS) questionnaire [20]. The questionnaire uses a 5-point Likert-style scale (ranging from "no change" to "complete resolution of the symptom"), and is an accepted primary tool used to assess efficacy in clinical trials with well-established psychometric properties, although not validated specifically for Parkinsonism [21]. The questionnaire included 22 items on various motor symptoms (tremor, rigidity, dyskinesia, freezing of gait, falls, balance, mobility, and off states) and non-motor symptoms (speech, swallowing, daytime sleepiness, dizziness, urinary impairment, constipation, mood, memory, hallucinations, sexual difficulties, and general function). The patient data on disease duration and Hoehn and Yahr (H&Y) scores were collected. The structured interview included questions on age at onset of symptoms, age at diagnosis, current medications, and frequency of IVAM infusions. The levodopa equivalent daily dose (LEDD) at baseline was calculated from the medications list. Patients were treated with oral amantadine 200 mg per day except for the days on which they were treated with IVAM.

STATISTICAL ANALYSIS

Based on the cohort of 30 patients and alpha established at 0.05, the calculated power of the study was 60% if minimal improvement was set at 70% and 80% if minimal improvement was set at 75%. This power applies to all variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics, including mean and standard deviation, were calculated for each variable. The response percentage was calculated for each symptom individually with no corrections for multiple comparisons. A *P* value < 0.05 was considered statistically significant.

RESULTS

Our study comprised 30 patients (12 females). Study population characteristics are described in Table 1. Among the patients, 19 were diagnosed with advanced PD, 2 with MSA, 2 with PSP, 2 with vascular Parkinsonism, 4 with Parkinsonism not specific, and one with diffuse Lewy body disease. The mean age was 73.3 ± 9.7 years, the average disease duration was 6.2 ± 5.7 years, and the mean H&Y score was 3.2 ± 0.84 . Prior to IVAM treatment, 25 patients were treated with levodopa and 3 patients were treated with oral amantadine. The five patients who were not treated with levodopa had atypical Parkinsonism. The average levodopa dose was 734 ± 388 mg/day. The mean duration of IVAM treatment was 15.1 ± 11.6 months (median 13, range 1–49 months). The number of IVAM infusions was 27.4 ± 22.2 (median 19, range 6–99 infusions).

Table 1. Study population characteristics

		(n)
Gender	Male 18; Female 12	
Age, years	73.3 ± 9.7	
Disease duration, years	6.2 ± 5.7	
Diagnosis (n)	PD (19) MSA (2) PSP (2) Vascular Parkinsonism (2) Parkinsonism not specific (4) Diffuse Lewy body (1)	
Hoehn & Yahr scores	3.2 ± 0.84	H&Y2 (6) H&Y3 (14) H&Y4 (8) H&Y5 (2)
LEDD (mg)	734 ± 388 mg	
Frequency of IVAM infusions (n)	Every week (2) Every 2 weeks (7) Every 3 weeks (21)	

H&Y = Hoehn and Yahr scores, IVAM = intravenous amantadine, LEDD = levodopa equivalent daily dose, MSA = multiple system atrophy, PD = Parkinson's disease, PSP = progressive supranuclear palsy

Overall, 91% (21/23) of the patients and 89% (16/18) of the caregivers reported improvement in general function with IVAM treatment in the CGICS questionnaire ($P < 0.05$). The majority of patients and caregivers reported improvement of motor symptoms, including tremor, rigidity, and reduced off time. In addition, the symptoms associated with gait, such as freezing of gait, balance and falls, and mobility also improved. Surprisingly, the extent of improvement in dyskinesia as reported by both the patients and caregivers was not significant. No improvement in any of the non-motor symptoms was reported. Importantly, the assessments of the patients and their caregivers were similar, despite their completing the questionnaires separately. The numbers of patients and caregivers who reported improvement in symptoms with IVAM treatment are given in Table 2.

Each of the side effects of confusion and hallucinations, leg edema, and excessive sleepiness, were reported by one patient, but they did not result in their dropping out of the study.

DISCUSSION

The data presented in this single-center study reflect the subjective responses of patients with advanced Parkinsonism to repeated IVAM infusions. Our patients were severely disabled individuals who were followed in a tertiary movement disorders center and received the best standard of care. Approximately 80% of these patients and their caregivers reported improvement in motor symptoms and, importantly, improvement in the symptoms associated with mobility (balance, freezing of gait, falls, and general mobility), which are disabling and usually refractory to dopaminergic treatment. Surprisingly, no significant improvement of dyskinesia was reported. The high

Table 2. Reported symptom improvement

	Patients reporting improvement, n	Patients reporting symptom, n	Patients reporting improvement, %
Tremor	13	17	76
Rigidity	16	21	76
Freezing of gait	16	18	89
Falls	15	19	79
Mobility	21	28	75
Off time	9	11	82
General function	21	23	91
Swallowing	6	10	60
Daytime sleepiness	10	15	67
Sexual function	2	13	15
Dyskinesia	5	8	63
Balance	19	27	70
Speech	9	17	53
Vertigo	6	11	55
Urinary disturbance	5	13	38
Constipation	4	20	20
Mood	8	15	53
Memory	5	16	31
Hallucinations	7	12	58

proportion of patients who reported improvement in motor symptoms is probably partially related to a placebo effect, which has been described in PD and was shown to affect multiple motor symptoms, including bradykinesia, rigidity, tremor, gait, and balance [22]. However, the close agreement between the patients and the caregivers in their impression of improvement associated with the treatment supports a true positive effect.

Motor improvement with oral amantadine therapy has been reported previously in randomized clinical trials [2]. However, an effect of IVAM on motor function was reported mostly in open-label or retrospective studies that were conducted several decades ago [14,23,24]. The effect of IVAM on freezing of gait was recently investigated in two controlled studies and it was not shown to significantly improve the overall freezing of gait questionnaire scores [18,19]. However, it was suggested that IVAM might be beneficial by attenuating freezing of gait severity and improving patient mobility. These conclusions concur with our results of the improvement of general mobility in our patients. Unexpectedly, no improvement of dyskinesia was reported by either the patients or their caregivers. That finding could be due to dyskinesia not being an especially disabling symptom among patients with advanced Parkinsonism, given that off rigidity and immobility are more debilitating than dyskinesia. Dyskinesia is usually problematic for caregivers, and we could expect some discrepancy between their responses

and those of the patients, but this was not the case. However, all of our patients were treated by oral amantadine in-between IVAM infusions, and this treatment may also explain the low burden associated with dyskinesia. Indeed, the overall burden of dyskinesia in our cohort could be expected to be relatively low since 11 of 30 of our patients had advanced Parkinsonism and only 19 had advanced PD.

Neither the patients nor their caregivers reported improvement in any of the non-motor symptoms other than “general function”. The literature on the effect of amantadine on non-motor symptoms is sparse, although one study did suggest a positive effect of amantadine on specific cognitive functions [15], which was not demonstrated in our study.

There were relatively few adverse effects of amantadine among our patients and they did not result in their dropping out from the study.

LIMITATIONS

First, this is a retrospective analysis of an open-label trial without a placebo-controlled group and thus bears the limitations of such a study design. It was not possible to neutralize a placebo effect whose rate averages around 16% (range 0–55 %), while patients with more advanced disease reportedly showed increased odds of a positive placebo response [25]. Furthermore, we have no reference group, which could strengthen our results. Second, only subjective effects of IVAM were assessed in this study by using the CGICS, in which psychometric characteristics were not tested in Parkinsonism. Validated objective measures (such as unified PD rating scale) were not incorporated in this study. Last, baseline demographic and comorbidities data may interfere with the results, since we report on a small and heterogeneous group of patients with different etiologies for advanced Parkinsonism who were treated with repeated IVAM in different time intervals. The daily intake of medication was not controlled with changes of LEDD or other medications throughout the study. All of these features make it difficult to perform more accurate characterization of the group, and impossible to perform multivariate analyses to assess the degree of benefit and the optimal time interval between infusions for each diagnosis, as well as to create the profile of the patients in whom IVAM could be most effective. Since the sample size of different types of Parkinsonism is very small, we did not attempt to assess the effect of IVAM in the different types of Parkinsonism, but rather chose a “symptomatic treatment” approach to the management. Further randomized clinical trials with a larger sample size using objective measures are warranted to validate our results.

CONCLUSIONS

To the best of our knowledge, this is the first attempt to assess the effect of repeated IVAM infusions on the function of

patients with advanced Parkinsonism who had been undergoing treatment for long periods of time. Subjective data were obtained from both the patients and their caregivers. Our findings suggest that repeated IVAM infusions could be effective and safe as an additional tool for the improvement of motor symptoms, balance and mobility as well as general function of the patients with advanced Parkinsonism. These patients have unmet needs, and there are currently no disease-modifying treatments for them. We suggest that they will be able to benefit from this safe non-levodopa treatment.

Correspondence

Dr. M. Kestenbaum

Dept. of Neurology, Meir Medical Center, Kfar Saba 4428164, Israel

Phone: (972-9) 747-1581,

Fax: (972-9) 747-1317

email: meirkes@gmail.com

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Capsule

Magnesium for *Salmonella* growth

In mammals, macrophages are a first line of defense against pathogenic bacteria like *Salmonella*. These immune cells possess a metal-ion transporter called SLC11A1 or NRAMP1, which is known to be involved in infection resistance. **Cunrath** and **Bumann** studied mice that only differ in one allele of the SLC11A1 gene, which leaves mice either susceptible or resistant to infection. Proteomic analyses showed that

bacteria isolated from mice with functional SLC11A1 alleles experienced metal starvation, particularly of magnesium. The resulting impairment of bacterial growth seems to be the primary mode of action of SLC11A1 against invading pathogens.

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Eitan Israeli

Capsule

Mixed signals at tumor margins

The Hippo signaling pathway has been implicated in tumor growth, sparking interest in the pathway as a potential therapeutic target. In a study of liver cancer in genetically manipulated mice, **Moya** and co-authors discovered that the role of this pathway in tumorigenesis is more complex than previously appreciated. They confirmed that activation of the Hippo pathway within tumor cells drives tumor growth;

however, they also found that activation of the pathway in adjacent healthy cells has the opposite effect, suppressing tumor growth. Whether tumor cells survive or are eliminated thus appears to depend on competing signals produced by the tumor and surrounding tissue.

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Capsule

New cell therapy fights brain tumors

An adoptive cellular therapy that expands clonal T cells could help fight deadly heterogeneous brain tumors, medulloblastoma, and glioblastoma. Working in mice, **Flores** and co-authors used dendritic cells expressing tumor RNA to expand polyclonal T cells that quickly react against a variety of different antigens within different brain tumors. Promising results were also obtained in a patient with recurrent

medulloblastoma. Although previous adoptive T cell therapies have proven effective against several advanced cancers, the current method could provide patients with effective T cell therapy for brain tumors.

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Eitan Israeli

“The function of education is to help you from childhood not to imitate anybody, but be yourself all the time”

Jiddu Krishnamurti (1895–1986), Indian philosopher, speaker, and writer