The Use of Amantadine HCL in Clinical Practice: A Study of Old and New Indications

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DISCLOSURE

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ABSTRACT

Since the discovery of the anti-dyskinetic properties of amantadine, there has been a renewed interest in its use. To evaluate its efficacy and tolerability, we performed a retrospective study of consecutive patients with Parkinson's disease (PD) who had received amantadine either as mono- or combination therapy for a 3-year period. We identified 41 patients. Nineteen (46%) experienced amantadine-related side effects. Eleven (27%) discontinued treatment before 1 year. Although dyskinesias improved (to some extent) in all patients after amantadine treatment, only 73.3% experienced improvement of motor symptoms. In conclusion, amantadine was effective in the treatment PD for at least 1 year in 40% of our patients.

INTRODUCTION

Amantadine has been used as an antiparkinsonian drug since 1969.[1] For several years its main indications have been the treatment of early Parkinson's disease (PD) or as adjunct therapy for more advanced PD patients on stable doses of carbidopa/levodopa. Recently, there has been a renewed interest in its use after discovery of its antidyskinetic effects.[2,3] There is limited published information as to its long-term use either as monotherapy or in conjunction with carbidopa/levodopa or other more recently introduced antiparkinsonian

agents.[4] Recent findings suggest that amantadine alone and as adjuvant to L-dopa can significantly improve clinical motor and, possibly, autonomic symptoms.[5] The Cochrane Database Systematic Review[6,7] and other evidence-based reviews on the management of PD[8] have concluded that, although amantadine is considered efficacious, there is insufficient evidence on its safety, long-term efficacy, and antidyskinetic properties. In order to further evaluate the long-term efficacy of amantadine for a variety of PD-related symptoms and its tolerability as monotherapy or as adjunct to other antiparkinsonian agents, we performed a retrospective study of PD patients who had been placed on this drug during a 3-year period.

METHODS

We studied the clinical variables of consecutive PD patients who had received amantadine HCL either as monotherapy or in combination with other antiparkinsonian agents between June 1997 and May 2000. All patients were diagnosed and followed-up at the Movement Disorders Clinic of the Department of Neurology of University of Miami, School of Medicine. We excluded patients who were lost to follow-up after initiation of amantadine and those whose charts were inconclusive. Analysis of the information included demographics, clinical characteristics, degree of improvement with amantadine, concurrent antiparkinsonian medications, and occurrence of side effects.

Only those patients who completed at least 1 year of treatment were included in the analysis for possible therapeutic benefits. Results of treatment were analyzed using a global impression scale (0=no improvement; 1=mild improvement; 2=moderate improvement; 3=marked improvement). We also analyzed side effects throughout the year including those instances where side effects prompted the discontinuation of treatment, as well as those side effects that patients were willing to tolerate due to benefits.

RESULTS

Demographics

We identified 41 patients with adequate follow-up information (Table 1). There were 19 males and 22 females. The mean age of our patients was 63.0 ± 9.2 years and the mean duration of Parkinson's disease was 8.2 ± 5 years. Mean Hoehn & Yahr was 2.2 ± 0.7. Five patients were on amantadine monotherapy. Thirty-six were on 1 or more concurrent antiparkinsonian medications (carbidopa/levodopa [n=27], pramipexole [n=3], selegiline [n=2], pramipexole and selegiline combined [n=4]). No patients were on levodopa plus additional dopaminergic agents other than amantadine.

Nineteen patients (46%) experienced side effects, including edema of the lower extremities, nausea, hallucinations, lightheadedness, and headache. Eleven of those patients (27%) discontinued treatment before 1 year of treatment had been completed. The other 8 patients (20%) continued treatment with amantadine for 1 year or longer in spite of the occurrence of side effects. Mean dosage of amantadine in patients who experienced side effects was 231.57 mg, compared to 277.27 mg in those free of side effects. We could therefore not find any relation between the dosage of amantadine and the presence of side effects.

Thirty patients (73%) completed at least 1 year of treatment with amantadine (Table 1). Targeted symptoms included the following: dyskinesias (n=13), motor symptomatology (n=15), wearing off (n=2), and freezing (n=3). There were 3 patients with more than 1 group of targeted symptoms (2 were

Table 1. Demographics and Side Effect Profile for Patients with Parkinson's Disease (PD) Treated with Amantadine, Comparing Those who Stopped Taking the Drug Before a Year Had Elapsed with Those who Completed a Year of Treatment.

	<1 year of amantadine	>1 year of amantadine
Number of patients	11	30
Age (yrs)	66.3 ± 8.1	61.8 ± 9.4
Gender		
Female (n=22)	8	14
Male (n=19)	3	16
PD duration (yrs)	6.4 ± 3.8	8.9 ± 5.2
Hoehn & Yahr	2.3 ± 0.7	2.2 ± 0.7
Concomitant treatment		
None	3 (27.3%)	3 (10%)
L-dopa alone	8 (72.7%)	18 (60%)
Other anti-PD medications (pramipexole, selegiline)	0	9 (30.0%)*
Amantadine dose (mg)	218.2 ± 87.4	276.7 ± 85.8
Side effects		
Hallucinations	1 (9.1%)	3 (10%)
Leg edema	4 (36.4%)	4 (13.3%)
Lightheadedness	2 (18.2%)	0
Nausea	2 (18.2%)	1 (3.3%)
Headache	1 (9.1%)	0
Indeterminate	1 (9.1%)	0

*3 patients were on pramipexole, 2 patients were on selegiline, 4 were on pramipexole and selegiline

treated for dyskinesias and freezing, 1 for dyskinesias and other PD symptoms).

Dyskinesias improved in all 13 patients, including moderate to marked improvement in 11 (Table 2). This effect was maintained during the entire year with small increases of the dosage of amantadine in some patients. In 1 patient, a concurrent decrease in dose of pramipexole may have helped in the amelioration of the dyskinesias. Parkinsonian motor symptoms (tremor, rigidity, bradykinesia) improved in 11 of the 15 patients (73%) (Table 2). Wearing-off phenomena improved in one half of the patients, and freezing improved in one third. There were only 3 patients on amantadine monotherapy, of which only 1 completed 1 year of treatment. Of the 30 patients who continued treatment for longer than 1 year, 24 (80%) experienced persistent improvement beyond the first year of treatment. We could not find any statistical relation between the degree of improvement and any of the following: age, duration of disease, H&Y stage, and mean dose of amantadine.

DISCUSSION

The goal of this study was to determine the efficacy of amantadine on parkinsonian symptoms and dyskinesias as well as its tolerability as seen in day-to-day practice at a tertiary referral center. Although the study has the known disadvantages of retrospective studies, it allows for an overview of "real-life" use of an old drug in a modern setting. To date, long-term studies have only reported on the use of amantadine concurrent-

Table 2. Effectiveness of Amantadine on Parkinson Disease (PD) Symptoms and Dyskinesias

	Dyskinesias*†	PD Symptoms†
Number of patients	13	15
No improvement	0	4 (26.7%)
Mild improvement	2 (15.4%)	3 (20.0%)
Moderate improvement	6 (46.2%)	6 (40.0%)
Marked improvement	5 (38.4%)	2 (13.3%)
Age (yrs)	64.9 ± 8.8	59.5 ± 10.1
PD Duration (yrs)	12.0 ± 3.8	5.3 ± 3.8
Hoehn & Yahr	2.5 ± 0.8	1.9 ± 0.5
Gender		
Female	5	8
Male	8	7
Amantadine dose (mg)	284.6 ± 68.9	266.7 ± 90.0

Three of the 30 patients are excluded from this table; 2 were treated for wearing off, 1 with no improvement and 1 with moderate improvement; 1 was treated for freezing with no improvement.
*2 patients also had freezing which was not improved in 1 patient and moderately improved in the other.
†1 patient is included in both the dyskinesia group and the PD symptoms group as they were treated for both.

ly with levodopa and/or anticholinergics.[9-12] The concurrent use of amantadine with other antiparkinsonian agents has never before been reported in the long-term evaluation of treatment of PD symptoms.

To analyze the effectiveness of amantadine in the treatment of dyskinesias and parkinsonian symptoms we only included those patients treated for more than 1 year. We found that amantadine induced a significant improvement in dyskinesias in the great majority of patients (11/15 [85%]). Our results are similar to those of Verhagen et al[3] who reported on 14 patients treated with amantadine a double-blind, placebo-controlled, cross-over study. In the 14 patients completing this trial, amantadine reduced dyskinesia severity by 60% (P=0.001) compared to placebo, without altering the antiparkinsonian effect of levodopa. They concluded, as we do, that the antidyskinetic effect of amantadine lasts at least 1 year.[3] Significant improvement of dyskinesias following amantadine treatment has been also reported by others.[13] Conversely, Paci et al's study showed that after 2-8 months of amantadine treatment, dyskinesias scores increased to the point of pretreatment scores.[14] A recent 12-month double-blind study designed to assess the duration of the antidyskinetic effect of amantadine on levodopa-induced dyskinesia found that the benefit of amantadine lasted less than 8 months.[4]

Concerning the response of parkinsonian symptoms to amantadine in 15 patients, 73% had some degree of improvement. Older patients and those with longer duration of PD experienced more improvement, although it did not reach statistical significance. We did not find any relationship between the dosage of amantadine and the degree of improvement. To maintain this improvement the dose of the dopamine agonist (pramipexole) had to be increased in 3 patients and L-dopa had to be added in 2 others. Amantadine was clearly effective for more than 1 year in 40% of the patients. These results are somewhat higher than those of Butzer et al[15] and Parkes et al[16] who found that 33% of patients maintained improvement, but

are similar to those of Thomas et al[4] who reported benefit in 45% of patients.

Amantadine was found to improve all parkinsonian symptoms. The improvement of pain was striking in 2 patients, an effect that has already been reported in patients suffering from neuropathic pain.[17,18] Amantadine has also been found effective in the control of parkinsonian motor symptoms especially when combined with L-dopa in non-white populations.[5]

Eleven patients could not be evaluated for effectiveness because they discontinued treatment in less than 1 year (27%). It is probable that in these patients side effects were combined with the lack of response to treatment.

Edema of lower extremities was present in 8 patients, hallucinations in 4, and nausea in 3. Four of the 8 patients who presented with edema were concurrently on pramipexole, which has also been associated with this side effect.[19] It is also of interest that a majority of those patients suffering from hallucinations chose to continue treatment. In 1 case, control of hallucinations with quetiapine allowed for continuation of treatment with amantadine. In general, of all patients who experienced side effects while on amantadine, a high percentage (42%) chose to continue receiving it. Other studies shows similar results.[11,16]

Our study has some inherent limitations commonly seen in retrospective series. There may be a referral bias as our sample is clinic-based and selection bias may have also occurred since some of the presented results were recorded in patients who completed 1 year of treatment. Furthermore, some of our findings rely on subjective ratings rather than validated clinical scales. However, all study patients have been evaluated and followed by the same movement disorders specialist (CS). Hence the impact of confounding factors such as inconsistencies in the diagnosis, inaccurate history, inter-examiner differences, and under-documentation of patient symptoms and side effects, were reduced. The small patient number also limits the power of our results.

CONCLUSION

In conclusion, amantadine was effective in the treatment PD-related symptoms for at least 1 year in 40% of our patients. Amantadine was found useful when used in conjunction not only with carbidopa/levodopa but with other agents such as pramipexole and selegiline. Amantadine was highly effective for dyskinesias for at least 1 year. In spite of a high incidence of side effects (46%), a substantial number of patients (42%) chose to continue treatment because of symptomatic improvement.

REFERENCES

1. Schwab RS, England AC Jr, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. *JAMA*. 1969;208:1168-1170.
2. Blanchet PJ, Konitsiotis S, Chase TN. Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Mov Disord*. 1998;13:798-802.
3. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, et al. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998;50:1323-1326.
4. Thomas A, Iacono D, Luciano AL, et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75:141-143.
5. Bandini F, Pierantozzi M, Bodis-Wollner I. The visuo-cognitive and motor effect of amantadine in non-Caucasian patients with Parkinson's disease. A clinical and electrophysiological study. *J Neural Transm.* 2002;109:41-51.
6. Crosby NJ, Deane KH, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. Cochrane Database Syst Rev 2003(2):CD003467.
7. Crosby N, Deane KH, Clarke CE. Amantadine in Parkinson's disease. Cochrane Database System Review. 2003(1):CD003468.

8. Goetz CG, Koller WC, Poewe W. Management of Parkinson's disease: an evidence-based review. *Mov Disord*. 2002;17(suppl 4):S1-166.

9. Schwab RS, Poskanzer DC, England AC Jr., Young RR. Amantadine in Parkinson's disease. Review of more than two years' experience. *JAMA*. 1972;222:792-795.

10. Savery F. Amantadine and a fixed combination of levodopa and carbidopa in the treatment of Parkinson's disease. *Dis Nerv Syst*. 1977;38:605-608.

11. Forssman B, Kihlstrand S, Larsson LE. Amantadine therapy in parkinsonism. *Acta Neurol Scand*. 1972;48:1-18.

12. Timberlake WH, Vance MA. Four-year treatment of patients with parkinsonism using amantadine alone or with levodopa. *Ann Neurol.* 1978;3:119-128.

13. Luginger E, Wenning GK, Bosch S, Poewe W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord.* 2000;15:873-878.

14. Paci C, Thomas A, Onofrj M. Amantadine for dyskinesia in patients affected by severe Parkinson's disease. *Neurol Sci.* 2001;22:75-76.

15. Butzer JF, Silver DE, Sahs AL. Amantadine in Parkinson's disease. A double-blind, placebo-controlled, crossover study with long-term follow-up. *Neurology.* 1975;25:603-606.

16. Parkes JD, Baxter RC, Marsden CD, Rees JE. Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1974;37:422-426.

17. Pud D, Eisenberg E, Spitzer A, et al. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain.* 1998;75:349-354.

18. Amin P, Sturrock ND. A pilot study of the beneficial effects of amantadine in the treatment of painful diabetic peripheral neuropathy. *Diabet Med.* 2003;20:114-118.

19. Tan EK, Ondo W. Clinical characteristics of pramipexole-induced peripheral edema. *Arch Neurol.* 2000;57:729-32.