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

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KEY WORDS: amantadine, dyskinesias, side-effects, clinical practice

DISCLOSURE
This work was supported in part by a grant from the National Parkinson Foundation (NPF #662891). This report was presented in part at the 7th International Congress of Parkinson’s Disease and Movement Disorders, Nov 10-14, 2002, Miami, FL.

Dr L. Vela was supported by the FIS (Fondo de Investigaciones de la Seguridad Social) Grant 01/5023.

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 anti-parkinsonian drug since 1969. 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. 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. Recent findings suggest that amantadine alone and as adjuvant to L-dopa can significantly improve clinical motor and, possibly, autonomic symptoms. The Cochrane Database Systematic Review and other evidence-based reviews on the management of PD 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
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-
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 al3 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 ant dyskinesinetic 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 pre-treatment 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 al15 and Parkes et al16 who found that 33% of patients maintained improvement, but

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Dyskinesias†</th>
<th>PD Symptoms†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>0</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Mild improvement</td>
<td>2 (15.4%)</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>6 (46.2%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>5 (38.4%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64.9 ± 8.8</td>
<td>59.5 ± 10.1</td>
</tr>
<tr>
<td>PD Duration (yrs)</td>
<td>12.0 ± 3.8</td>
<td>5.3 ± 3.8</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.5 ± 0.8</td>
<td>1.9 ± 0.5</td>
</tr>
</tbody>
</table>

†1 patient is included in both the dyskinesia group and the PD symptoms group as they were treated for both.

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

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.
are similar to those of Thomas et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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**


