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Brief Report

Amantadine Is Beneficial in Restless Legs Syndrome

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Summary: Twenty-one patients (mean age 70 yrs) with restless legs syndrome (RLS) were treated with amantadine in an open-label trial. Amantadine was started at 100 mg per day and was increased every 3–5 days by 100 mg (up to a maximum of 300 mg per day) until significant relief of symptoms or intolerable side effects were experienced. Patients were rated pre- and posttreatment using an RLS rating scale (0–10). Each patient also rated the degree of response in a continuous scale from 0% (no improvement) to 100% (complete improvement). Eleven of 21 (52%) had subjective benefit to amantadine, with degree of response ranging from 25%–100% (mean 69%) among responders. Six had 95%–100% improvement. The RLS score for all 21 patients dropped from a mean (± standard deviation) of 9.8 ± 0.6 (range, 8–10) pretreatment to 6.6 ± 3.8 (range, 0–10) posttreatment ($p = 0.001$). The duration of response was 0–13 months (mean, 3.6 ± 4.5), with nine responders still remaining on the drug as of last follow up. The mean effective dose was 227 mg per day. The most common side effects were drowsiness (3), fatigue (2), and insomnia (2); only two stopped amantadine because of side effects. We conclude that amantadine is an effective and well-tolerated drug for RLS.
Key Words: Restless legs syndrome—RLS—Amantadine.

Restless legs syndrome (RLS) is characterized by paresthesias or dysesthesias, a desire to move the limbs, nocturnal exacerbation or appearance of symptoms, motor restlessness, periodic limb movements, and sleep disturbance.[1,2] Despite its common occurrence (10%–15% of the general population),[3] RLS is often unrecognized and misdiagnosed, leading to significant physical and emotional disability. Although the exact etiology of idiopathic RLS is unknown, dopaminergic dysfunction is postulated based on the favorable response of RLS to antiparkinsonian medications like levodopa and dopamine agonists.[2] Amantadine is a drug that was developed for the prophylaxis and treatment of influenza A,[4] but was serendipitously discovered to be effective in patients with Parkinson's disease (PD).[5] The exact mechanism by which amantadine benefits patients with PD is unknown, but may involve an effect on cerebral dopamine metabolism, anticholinergic effects, or N-methyl-D-aspartate (NMDA) receptor antagonism.[6–8,11–14] We now report our open-label experience with the use of amantadine in patients with RLS.

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PATIENTS AND METHODS

Patients

Twenty-one patients (13 of 21 or 62% of which were female) were recruited from February 1997 to January 1998, with last follow up being in May 1998. The mean age was 70 ± 9 years (range, 46–84 yrs). The mean duration of RLS symptoms was 18 ± 17 years (range, 1–60 yrs). Eight of 21 patients (38%) had signs of peripheral neuropathy on clinical examination, two of whom had electromyography (EMG) confirmation of polyneuropathy. None had iron deficiency (based on fer-

ritin levels) or PD. The rest of the patient characteristics are outlined in Table 1.

Dosing of Medications

Amantadine was initiated at a dose of 100 mg per day and was increased by 100 mg every 3–5 days until a maximum dose of 300 mg per day was reached, intolerable side effects developed, or significant relief of symptoms was experienced. For patients with symptoms that started at bedtime, amantadine was given before sleeping. For patients with symptoms earlier during the night, amantadine was administered 1–2 hours before the usual onset of their RLS in the evening and, if necessary, another dose before sleeping. For individuals with daytime symptoms, amantadine was given 1–2 hours before the usual onset of their daytime symptoms, plus one or two more doses later during the day or night as needed. Seventeen patients were concurrently on other RLS medications (Table 2). The patients were instructed not to change the doses of these other RLS drugs during the entire duration of the study.

Outcome Variables

Patients were rated on a RLS rating scale (0–10) pretreatment and posttreatment with amantadine.[9] This RLS scale evaluates the following factors: frequency of RLS symptoms (0 = never, 1 = less than once a month, 2 = less than once a week, 3 = at least once a week, 4 = almost every night); severity (0 = no distress, 1 = mild, 2 = moderate, 3 = severe); and duration of symptoms (0 = no time or a few seconds, 1 = <30 minutes, 2 = >30 minutes but <1 hour, 3 = >1 hour).[9] Each subject was also asked to rate his or her response to amantadine on a continuous scale from 0% (no improvement) to 100% (complete resolution of symptoms).

TABLE 1. *Patient characteristics (N = 21)*

	No. (%)
Augmentation with levodopa	7 (33)
Polypharmacy for RLS	5 (24)
De novo	4 (19)
History of at least 2 ineffective drugs	12 (57)

RLS, restless legs syndrome.

Statistical Methods

The primary outcome variables were the change from baseline RLS score and the subjective RLS improvement rating. Posttreatment RLS scores were compared with the pretreatment scores using Wilcoxon's signed rank

TABLE 2. *Summary of patient data*

Patient no.	Pre-tx RLS score	Post-tx RLS score	Duration of response (mos)	Percent subjective response	Amantadine dose (mg/day)	Concurrent medications pre-tx
Responders						
1	10	0	6+	100%	100	None
2	10	5	13+	50%	200	Levodopa
3	10	8	2	25%	300	Levodopa
4	10	5	3+	50%	300	Levodopa
5	10	2	10+	97%	200	Levodopa
6	9	0	13+	95%	200	Lorazepam
7	10	0	9.5+	100%	200	Levodopa; clonazepam; diazepam
8	10	7	5+	25%	300	Pergolide
9	8	6	2.5+	30%	200	None
10	10	2	6+	95%	300	None
11	10	5	5	95%	200	Levodopa; hydrocodone
Nonresponders						
12	10	10	0	0	300	Levodopa
13	10	10	0	0	200	None
14	8	8	0	0	300	Levodopa
15	10	10	0	0	300	Levodopa; gabapentin; clonazepam
16	10	10	0	0	100	Gabapentin
17	10	10	0	0	200	Propoxyphene
18	10	10	0	0	100	Levodopa
19	10	10	0	0	100	Lorazepam; clonazepam; levodopa
20	10	10	0	0	300	Aspirin; acetaminophen
21	10	10	0	0	300	Levodopa

Pre-tx, pretreatment; Post-tx, posttreatment.
+ Continuing response.

TABLE 3. *Restless legs syndrome score (N = 21)*

	Pretreatment	Posttreatment	Change	p value*
Mean	9.8	6.6	−3.2	0.001
SD	0.6	3.8	3.8	
Minimum	8	0	−10	
Median	10	8	−2	
Maximum	10	10	0	

* p value is from Wilcoxon's signed rank test.

test. Subjective RLS improvement ratings were compared with 0 using Wilcoxon's signed rank test. The relationship between the change in RLS score and the subjective RLS improvement rating was assessed using Pearson's correlation. The coefficient of variation or CV (the standard deviation divided by the mean) was used to assess which of the two primary outcome measures had greater precision (smaller CV is preferred). The association between the subjective RLS improvement rating and the baseline characteristics was assessed using multivariable general linear modeling with a forward stepwise selection procedure. Potential predictors of the subjective RLS improvement rating were also assessed in a univariate fashion using Pearson's correlation for the continuous baseline characteristics and Wilcoxon's rank sum test for the binary baseline characteristics.

RESULTS

The RLS scores are summarized in Tables 2 and 3. Posttreatment RLS scores were statistically significant lower than the pretreatment scores ($p = 0.001$ using Wilcoxon's signed rank test). The median reduction was 2 points (range, 0 to 10) on the 10-point scale. Eleven of 21 patients (52%) had subjective benefit from amantadine for RLS. The subjective RLS improvement ratings had a median of 25% (range, 0%–100%), and were significantly larger than zero ($p = 0.001$ using Wilcoxon's signed rank test). Among the responders, the perceived response ranged from 25%–100% (mean, 69%). Six of the responders had 95% or more improvement, three of whom had complete resolution of their RLS. Two responders were able to wean themselves completely off their levodopa. The duration of response for the entire cohort varied from 0–13 months, with nine responders still benefiting from the drug as of last follow up (range, 2.5–13 mos). One individual, with the most severe peripheral neuropathy among the 21 patients, lost benefit after 2 months of amantadine therapy and was shifted to another medication. Among the 11 responders, the effective dose was 100 mg per day for 3, 200 mg per day for 4, and 300 mg per day for 4 (mean, 227 mg per day). Five nonresponders decided to pull out of the study before reaching the maximum dose of 300 mg per day because of severe symptoms (pretreatment RLS score = 10) unresponsive to the lower doses of amantadine. A family history of RLS was present in five responders and five nonresponders.

The changes in RLS scores were strongly correlated with the subjective RLS improvement ratings ($r = 0.97$, $p < 0.001$). The precision of the change in RLS score (CV = 1.19) was nearly equal to that of the subjective improvement rating (CV = 1.17).

No statistically significant predictors of the subjective RLS improvement rating were identified using the forward stepwise general linear modeling procedure. However, this was a secondary analysis and statistical power was low. Univariate assessment of the baseline characteristics as potential predictors of the subjective RLS improvement did not yield any statistically significant results. However, the mean subjective RLS improvement rating for patients without levodopa augmentation (mean, 49%) was nearly 4.5 times that for patients with levodopa augmentation (mean, 11%). Patients with a history of no more than one ineffective RLS drug had a mean subjective RLS improvement rating (mean, 52%) that was twice as large as that for those with a history of two or more ineffective RLS drugs (mean, 25%). The correlations of subjective RLS improvement rating versus age ($r = -0.10$, $p = 0.68$) or versus duration of RLS ($r = -0.10$, $p = 0.68$) were both low.

None of the patients developed augmentation (earlier onset of symptoms during the evening, shorter latency to onset after assuming a restful position, increased intensity of symptoms, or extension of the symptoms to the upper body) or rebound (increase in severity of symptoms in the morning) with amantadine, even with long-term use.[2] The side effects of amantadine included drowsiness (3), fatigue (2), insomnia (2), dry mouth (1), leg edema (1), and weight loss (1). Two patients (both responders) stopped amantadine because of side effects: one stopped at 5 months because of leg edema and the other at 3 months because fatigue, drowsiness, and weight loss.

DISCUSSION

Our results show that amantadine may be an effective treatment for RLS. Although a placebo effect cannot be ruled out in any open-label trial, the almost complete resolution of symptoms in six individuals and the continued long-term benefit in nine suggest that amantadine is effective in RLS, even in severe cases. Although no potential predictors of subjective RLS improvement rating were statistically significant in this study, there was a trend for the presence of augmentation with levodopa or a history of at least two ineffective RLS drugs in the

past to predict poorer response to amantadine therapy. Like other RLS medications, some patients may develop tolerance to amantadine after several months. Three of our responders shifted to some other drug within the first 6 months of therapy (one because of loss of benefit and two because of side effects). Amantadine can also offer long-term benefit in RLS without diminution of effect or development of tolerance. Two patients have had more than 1 year's benefit so far. Amantadine is, in general, a well-tolerated drug. Only two of 21 individuals stopped the medication because of side effects.

Augmentation and rebound were not observed in any of the responders to amantadine. Although levodopa is an extremely effective medication in RLS, approximately 80% will develop augmentation as early as a few months after initiating the drug.[10] Our data suggest that amantadine may be a good alternative in weaning patients with RLS off levodopa to minimize the development of augmentation from the latter.

The mechanism of action of amantadine in RLS is uncertain. In PD, amantadine is thought to work by increasing synthesis/release or decreasing presynaptic reuptake of dopamine, or by exerting direct cholinergic or N-methyl-D-aspartate (NMDA) receptor antagonism.[11,12] NMDA antagonism can also lead to enhanced dopamine release and turnover[13] and decreased release of acetylcholine.[14] Dopaminergic dysfunction is a likely cause of RLS because dopamine blockers reactivate symptoms in treated patients[15] and deficiency of D2 dopamine receptors is observed in single photon emission computed tomography scans.[16] Cholinergic or NMDA receptor abnormalities have not been directly implicated in RLS. However, given the indirect dopaminergic effects of cholinergic or NMDA antagonism, amantadine, through any of its three possible mechanisms of action, may benefit patients with RLS.

In conclusion, our open-label study suggests that amantadine may be an effective treatment for RLS, even in patients with severe symptoms. Amantadine may remain beneficial even with long-term use and tolerance was infrequent. Because the treatment of RLS often involves trying one drug after another (until an effective drug is discovered) and because dopaminergic agents are among the most effective agents in treating patients with RLS, amantadine should be considered as an effective alternative in RLS, both as monotherapy and as add-on therapy. Additional studies using a double-blind, placebo-controlled design, as well as development and use of an RLS scale that can record both improvement and worsening, are indicated to validate our findings.

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