Amantadine's role in the treatment of levodopa-induced dyskinesia

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Levodopa-induced dyskinesia (LID) is one of the most common and frequently dose-limiting complications of pharmacologic therapy for Parkinson disease (PD). These typically choreiform movements, usually occurring at the time of peak levodopa effect, occur in 40% to 50% of patients after 5 years of therapy but have a reported incidence as high as 94% in a carefully conducted prospective study of patients under treatment for 15 years.[1] When mild, LID often goes unnoticed by patients, but moderate or severe forms frequently constitute a major motor or emotional disability. This can lead to reduction or discontinuance of otherwise effective PD therapies and may prompt implementation of more invasive treatments such as deep brain stimulation or direct intrajejunal infusion of levodopa gel. The need for a safe, effective, and enduring means of combating LID is clear. Although many drugs have been evaluated for this purpose and others are currently under investigation, to date only one agent, amantadine, has been effective in an evidence-based medicine review.[2]

Amantadine was originally developed in the 1960s for treating influenza but soon after was serendipitously found to be mildly effective for PD. Still later, in the late 1990s, small clinical trials and common clinical experience suggested its ability to alleviate LID. It is a complex drug with a variety of actions, some of which are still not totally understood. Figuring out how it suppresses LID is further complicated by the fact that the precise mechanism(s) of LID has not been fully elucidated. LID seems to be associated with abnormalities in presynaptic dopamine release, as well as delayed postsynaptic effects[3] that may involve medium spiny neurons expressing D-1 dopamine receptors in the direct pathway of the striatum.[4] Glutamate receptors appear to have a role in the pathogenesis of LID, in part by promoting synaptic changes seen in striatal neurons, thereby providing a scientific rationale for the use of amantadine, a weak NMDA inhibitor, to treat this complication. Amantadine may inhibit LID by decreasing glutaminergic cortical input to striatal neurons.[5] More potent NMDA inhibitors have not been well tolerated in human clinical trials.

Despite substantial clinical and scientific evidence supporting amantadine's efficacy in treating LID and the drug's widespread acceptance for this purpose, one aspect of its utility has continued to be questioned: its staying power. The notion that amantadine typically loses efficacy after a short period of administration has gained traction, in part because of an early study that suggested a loss of benefit after only 8 months.[6] This belief probably inhibits its use by some clinicians.

In this issue of *Neurology*®, Ory-Magne et al.[7] present Class II evidence from the multicenter French AMANDYSK (AMANtadine for DYSKinesia) trial that amantadine can retain its antidyskinetic properties over several years. Fifty-seven dyskinetic patients with PD, having been treated with amantadine for an average of 3.4 years, were studied utilizing a 3-month, parallel, washout design. Patients were randomized to either continue on amantadine or have it withdrawn and replaced by placebo. The primary outcome measure, determined 3 months after this intervention, was a dyskinesia score derived from the sum of 2 Unified Parkinson's Disease Rating Scale items that assess dyskinesia severity and duration. This score increased (worsened) more in patients assigned to placebo compared with those continuing on amantadine therapy. Secondary outcome measures, including the Abnormal Involuntary Movement Scale, the number of patients who withdrew because of worsening LID, and the number of daily hours spent ON with troublesome dyskinesias, all reflected a greater deterioration in those patients withdrawn from amantadine.

These results suggest that amantadine has a long-lasting beneficial effect on LID. However, there are some features of the study design that detract, albeit minimally, from this conclusion. A recent study evaluated several methods of quantifying the severity of LID and found the Unified Dyskinesia Rating Scale to be the most sensitive, in part because it incorporates both patient-initiated and objective examiner ratings of dyskinesias.[8] In the AMANDYSK study, the Abnormal Involuntary Movement Scale, an

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objective measure of dyskinesia severity, was a secondary outcome measure. Furthermore, amantadine is associated with 2 easily identified cutaneous adverse effects, livedo reticularis and pedal edema. The disappearance or improvement of a sign, coincident with blinded withdrawal of the drug, risks compromising the blind. While the authors suggest that this was unlikely to have occurred, it would seem prudent for the baseline presence of these cutaneous manifestations to be considered exclusion criteria in a blinded withdrawal study involving this drug. As the authors point out, this study was conducted in an "enriched" population of patients who remained under treatment with amantadine for at least 6 months and for an average of 3.4 years. Conversely, those patients who may have discontinued treatment because of loss of efficacy at a much earlier stage of their illness were not included in the study population, making it somewhat more difficult to generalize the results to all PD patients with dyskinesias. On balance, however, this clinical trial makes an important therapeutic point. The confirmation that some PD patients with LID can derive benefit from amantadine for years will be extremely useful for clinicians managing these complex cases. Most importantly, these results should help put to rest any long-standing concerns about a uniformly short duration of amantadine's effect on LID and help inform practitioners not to preemptively and unnecessarily discontinue the drug.

AUTHOR CONTRIBUTIONS

Robert L. Rodnitzky: drafting/revising the manuscript. Nandakumar S. Narayanan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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