Murat Kürtüncü
İstanbul University Faculty of Medicine, Department of Neurology, İstanbul, Turkey

Amantadine's Effect in Levo-dopa Dependent Dyskinesia

Levo-dopa dependent dyskinesia (LDD) is a condition that occurs at the advanced stages of idiopathic Parkinson disease (IPD) that is very difficult to treat under some circumstances. Non-dopaminergic as well as dopaminergic pathways are thought to be responsible for the pathophysiology of LDD.

There is evidence suggesting that amantadine, which is an NMDA/glutamate receptor blocker and also the only pharmacological agent used for LDD, can prolong life expectancy in IPD (1). However, there have been conflicting results on the anti-dyskinetic efficacy of amantadine. There are studies showing that its effect gets weaker over the course of a few months and terminating the drug use does not cause a difference (2,3).

In "Amantadine for diskinesia" (AMANDYSK) study by Ory-Magne et al., the effect of termination on the peak dose dyskinesia has been investigated (4). This study, funded by French Ministry of Health, included patients from 8 centers in France who were using amantadine for at least 6 months, with 200 mg/day or more. The study also included patients who had undergone subthalamic deep brain stimulation. People who used subcutaneous apomorphine injection, antipsychotic or cholinesterase inhibitors were excluded from the study.

The patients were randomized in a double-blind, placebo-controlled setting to use 100 mg/day amantadine or placebo for 3 months, with 1:1 ratio. The placebo patients who were stopped from amantadine were switched to a dose of 100 mg every other day. The first end point of the study was determined as the score on "Unified Parkinson's Disease Rating Scale's" (UPDRS) 4th section, which is composed of dyskinesia subscales, at the last visit as compared to the baseline.

The study included 57 patients and except for slightly younger age in the amantadine group (61.3 versus 66.4, p=0.01), there were no difference found in terms of clinical properties. Twenty-nine patients terminated the drug trial early and the biggest portion of these patients were the ones who were in the placebo group whose LDD worsened after stopping amantadine.

At the end of the study, it was seen that dyskinesia scores in the placebo group were higher than the amantadine group. This difference remained statistically significant after correcting for amantadine's dose, treatment duration, dyskinesia score, age and L-dope dosage. In the patients who terminated treatment, there was an average of 2.5 points increase in the UPDRS' dyskinesia subscales. Abnormal Involuntary Movement Scale (AIMS) scores were also higher in the group that stopped the treatment.

In conclusion, AMANDYSK study, despite the small sample size, suggests that stopping amantadine in LDD leads to worsened symptoms in a matter of few days. This situation shows that the drug does have anti-dyskinetic effect and this result is in conflict with another study (2). The reason of this difference might be that AMANDYSK study focused on peak dose dyskinesia whereas the other study focused on biphasic dyskinesia for which amantadine is known to be less effective.

Two issues deserve attention among the conclusions of the study. First, UPDRS motor scores and the "off" duration has not changed despite amantadine was stopped. This might suggests that amantadine may not have a great effect on IPD's cardinal symptoms. Second issue is related to the drug's effect on chronic fatigue and apathy. Interestingly, while the anti-apathy effect of the drug was not observed based on the patient reports, it is visible in the reports of the caretakers. Amantadine can also affect chronic fatigue. The non-motor effects of the drug deserve more attention in the coming years.

References

1. Uitti RJ, Rajput AH, Ahlskog JE, et al. Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. Neurology 1996;46:1551–1556.
2. 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.
3. Wolf E, Seppi K, Katzenschlager R, et al. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. Mov Disord 2010;25:1357–1363.
4. Ory-Magne F, Corvol JC, Azulay JP, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. Neurology. 2014;82(4):300-7.

A New Approach to Neuromyelitis Optical Treatment: Tocilizumab

Neuromyelitis optica (NMO) is a disease involving primarily optical nerve and spinal cord, driven by anti-aquaporin4 (anti-Aqp4) antibodies in its pathogenesis. It mostly concerns humeral immunity. Numerous studies showed increase of IL-6 in CSF and serum during NMO attacks.

Address for Correspondence/Yazışma Adresi: Murat Kürtüncü MD, İstanbul University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
E-mail: kurtuncum@gmail.com

Tocilizumab (Actemra®), which has received approval for treatment of rheumatoid arthritis, is a monoclonal antibody produced against IL-6 receptors. Araki et al. investigated the effect of this drug on NMO in a study made in Japan (1). Researchers gave 8mg/kg tocilizumab once a month in addition to steroid or immunosuppressant treatment using 7 NMO patients. All of the patients were active cases who had at least 2 attacks within one year of the study.

Five out of seven patients who were on tocilizumab treatment were seen to go in remission. In patients who showed relapse, the severity of the relapse seemed to be mild and the attacks improved completely with the addition of steroid treatment. Treatment caused the mean annual relapse rate from 2.9±1.1 to 0.4±0.8 and also markedly decreased EDSS scores (from 5.1±1.7 to 4.1±1.6). While the radiological and electrophysiological findings of the patients did not change significantly after treatment, there was a decrease in the serum anti-Aqp4 levels. The study showed no severe side affects besides upper respiratory infection, acute enterocolitis, pyelonephritis, leukopenia, lymphopenia, anemia and a mild decrease in systolic blood pressure. Tocilizumab also allowed the doses of azathioprine and steroid treatment to decrease.

Interestingly, the most treatment-resistant pain showed improvement after tocilizumab treatment. Pain in three patients out of six disappeared after 12 months. This finding might suggest that IL-6 receptors might play a role in the pathophysiology of the neuropathic pain seen in NMO.

Reference

1. Araki M, Matsuoka T, Miyamoto K, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology. 2014;82(15):1302-6.

Comparison of Pramipexole and Pregabalin Treatments in Restless Leg Syndrome

Restless leg syndrome (RLS) is a disease characterized by restlessness and the desire the move the lower extremities during resting state, often at night. Its causes are poorly understood. The incidence rate in the populations of West Europe and America are 2-3%. The symptoms are alleviated by L-dopa and transient dopamine agonists ropinirole and pramipexole. However, one third of the patients, especially those who used dopamine agonists reported their complaints getting worse in the following years.

Allen et al. investigated the efficacy of pregabaline, which binds to the α (2) δ sub-unit of voltage-gated calcium channels with high affinity and used frequently in the treatment of neuropathic pain, in RLS (1). The researchers randomized medium-severe primary RLS patients to receive the 52-week-long treatment.

Seven hundred nineteen patients were divided into 4 groups. One group received pramipexole 0.25 mg/day, second one 0.5 mg/day, third one pregabaline 300 mg/day and the third one received placebo. At the end of 12 weeks, placebo group was randomized into one of the 3 active treatment groups. For the inter-group comparisons, International Restless Leg Syndrome Study Group Rating Scale (IRLS) and Clinical Global Impression of Improvement Scales (CGI-I) were used.

At the end of 12 weeks, IRLS values of the pregabaline group were decreased by an average of 4.5 points as compared to placebo group ($p<0.001$). In addition, the ratio of clinically improved patients to others was higher in the pregabaline group in comparison to placebo (71% versus 47%, $p<0.001$). When placebo group was compared to pramipexole 0.5 mg/day group was lower in IRLS score and CGI-I evaluation whereas there was no significant decrease in the 9.25 mg/day group. When pramipexole and pregabaline 0.5 mg/day groups were compared, IRLS scores were lower in pregabaline group at the 12th and 52nd weeks ($p<0.001$).

While 2.1% of pregabaline patients had worsening symptoms, 5.3% of those who used pramipexole 0.25 mg/day and 7.7% of those who used pramipexole 0.5 mg/day had that effect ($p=0.01$). The ratio of patients terminating treatment due to side effects was lower for pramipexole group compared to pregabaline group (18.5% for pramipexole 0.25 mg/day group, 23.9% for 0.5 mg/day group, 27.5% for pregabaline group). In addition, there were smaller increase in complaints in pregabaline 300 mg/day group compared to both pramipexole groups at 12th week, and compared to only 0.5 mg/day group at 52nd week.

Another important observation from the study is the connection between the increase in complaints and treatment. The fact that the groups differed in that sense supports this theory. In addition, the increase in complaints in pramipexole 0.5 mg/day despite the fact that it is more effective compared to 0.25 mg/day, suggests that this may be due to treatment. Pregabaline 300 mg has been just as effective as 0.5 mg pramipexol without as many side effects.

The increase complaints also seem to be related to the duration of the treatment. At the end of the study, this was seen in 6.6% of pramipexole 0.25 mg group, 9% in pramipexole 0.5 mg group and 1.7% in pregabaline group.

The use of dopaminergic treatment in RLS suggested a dopaminergic component in the pathogenesis of the disease. However, the fact a pregabaline, which has no effect on that system, had that efficacy for RLS suggested the need for new theories for the pathogenesis of the disease. Another interesting finding was that there were no differences between pramipexole 0.25 mg and placebo in terms of IRLS and CGI-I parameters.

Reference

1. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014;370(7):621-31.