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Long-Term Effects Of Olanzapine in Various Movement Disorders

Çeşitli Hareket Bozukluklarında Olanzapin'in Uzun Süreli Etkileri

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ABSTRACT

Objective: The aim of this retrospective study was to investigate the efficacy of olanzapine in long-term treatment in various hyperkinetic movement disorders.

Methods: Twelve patients with various hyperkinetic movement disorders (mean age, 47.4±14.5 years; mean disease duration, 9.08±7.01 years) received olanzapine. Patients with chorea due to Huntington's disease, tardive dystonia, oromandibular dystonia, post-ischemic hemidystonia, hemiballismus and post-traumatic rubral tremor were included in the study. The effects of treatment were assessed after treatment initiation according to the findings of the general clinical observation at visits with 6-month intervals.

Results: The mean follow-up time was 24 months and the mean olanzapine dose was 11.2±5.1 mg/day (median 10 mg/day). The mean general clinical observation degree was 2.4±0.5 (moderate improvement). Four patients were scored +3 on the general clinical observation degree (marked improvement).

The improvement of the general clinical observation degree was significant at 24-month olanzapine treatment (p=0.05).

Conclusion: Olanzapine may be used for the treatment of a large variety of hyperkinetic movement disorders. This is a long-term study on the effects of olanzapine in various hyperkinetic movement disorders. No serious side effects were reported. *(Archives of Neuropsychiatry 2010; 47: 213-5)*

Key words: Long-term effects, olanzapine, hyperkinetic movement disorders

ÖZET

Amaç: Bu retrospektif çalışmada, çeşitli hiperkinetik hareket bozukluklarında olanzapin'in uzun süreli tedavideki etkinliğini incelemek amaçlanmıştır.

Yöntemler: Çalışmaya toplam 12 çeşitli hiperkinetik hareket bozukluğu hastası (ortalama yaş 47.4±14.5 yıl, ortalama hastalık süresi 9.08±7.01 yıl) alınarak olanzapin tedavisi verildi. Hasta grubuna, Huntington hastalığına bağlı kore, tardiv distoni, oromandibuler distoni, iskemi sonrası hemidistoni, hemiballismus ve travma sonrası rubral tremor tanılı hastalar dahil edildi. Değerlendirmeler 6 aylık aralarla hastaların tedavi sonrasındaki vizitlerdeki genel klinik izlemlerine göre yapıldı.

Bulgular: Hastalar ortalama 24 ay izlendi ve ortalama olanzapin dozu 11.2±5.1 mg/gün idi. Ortalama genel klinik izlem derecesi 2.4±0.5 (orta derecede iyileşme) idi. Toplam 4 hastanın ortalama genel klinik izlem derecesi +3 (belirgin iyileşme) idi. Olanzapin tedavisinin 24. ayındaki ortalama genel klinik izlem derecesindeki iyileşme belirgindi (p=0.05).

Sonuç: Olanzapin, çok çeşitli hiperkinetik hareket bozukluklarının tedavisinde kullanılabilir. Bu çalışma, çeşitli hiperkinetik hareket bozukluklarında olanzapin'in etkilerinin incelendiği uzun süreli bir çalışmadır. Tedaviye bağlı ciddi yan etkiler gözlenmemiştir. *(Nöropsikiyatri Arşivi 2010; 47: 213-5)*

Anahtar kelimeler: Uzun süreli etkiler, olanzapin, hiperkinetik hareket bozuklukları

Introduction

Dopamine receptor blocking agents (neuroleptics) are effective drugs for hyperkinetic movement disorders (1,2). However, antidopaminergic drugs are problematic because of affective and cognitive side-effects, as well as a real risk for the development of parkinsonism or tardive syndromes (1). Due to their new pharmacologic profile, atypical neuroleptics may be a better alternative for these problems. Olanzapine, a serotonin-dopamine receptor antagonist, is an atypical antipsychotic drug used in the treatment of schizophrenia (3). Olanzapine has been used in various movement disorders: choreic syndromes [Huntington's disease (HD), hemichorea] (1,4,5,6,7), tardive dystonia (8,9,10), tardive dyskinesia (9,11,12), hemiballismus (13), dystonia (14,15), and essential tremor (16,17).

We report the effect of olanzapine in the treatment of a group of patients with various hyperkinetic movement disorders.

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Methods

Twelve patients with various hyperkinetic movement disorders (6 women, 6 men), with a mean age of 47.4±14.5 (range:22-78) years and with a mean disease duration of 9.08±7.01 years (range: 1-25), received olanzapine in this study. The retrospective study was performed based on the findings of the general clinical observation at follow-up visits after treatment. The patients were chosen from those admitted to the movement disorders out-patient clinic between 2002 and 2008. All patients underwent detailed neurologic history and examination. They experienced severe involuntary movements in the form of chorea or dystonia or ballism or tremor and they did not respond to appropriate prior other medical treatments (anticholinergics, conventional neuroleptics, benzodiazepines). Olanzapine was prescribed at a starting dose of 2.5-5 mg/day and it was increased to a maximum of 20 mg/day because of resistance to many drug therapies. All patients were interviewed (at their follow-up visits) regarding treatment duration, dose, effect of treatment, and side effects. Patients were evaluated based on the findings of the general clinical observation at visits after 3 months of treatment initiation and at 6 months intervals. The general clinical observations were extracted from the charts of the patients. The grading in general clinical observation was as follows: +3:marked improvement, +2:moderate improvement, +1: mild improvement, 0: no change, -1:mild worsening, -2: moderate worsening, -3:marked worsening (1,2). Data regarding patient age, gender, diagnosis, and disease duration were extracted from their charts. SPSS version 11.5 for Windows was used for statistical testing. Variables are presented as a mean value ± SD. Within-group comparisons of the differences in the general clinical observation degrees between baseline and 6/24 months after olanzapine treatment were evaluated using the nonparametric Wilcoxon signed rank test.

Results

Patient distribution was as follows: Seven patients had chorea due to HD, 1 had tardive dystonia, 1 had oromandibular dystonia (OMD), 1 had post-ischemic hemidystonia, 1 had hemiballismus, and 1 patient had post-traumatic rubral tremor. Ten patient observations were included in the study period. The mean treatment length in ten patients was 24 months and the mean olanzapine dose/day at the last assessment was 11.2±5.1 mg/day (median 10 mg, range: 5-20 mg/day). The mean improvement of general clinical observation degree was 1±2 (mild improvement) at 6 months. The mean improvement of general clinical observation degree was 2.4±0.5 (moderate improvement) at 24 months. There was a statistically moderate improvement in the general clinical observation degree between baseline and 6 months after olanzapine treatment (Wilcoxon signed rank test, p=0.06). There was a statistically significant improvement in the general clinical observation degree between baseline and 24 months after olanzapine treatment (Wilcoxon signed rank test, p=0.05). The six patients had moderate and four had marked improvement of general clinical observation degree. The group with marked improvement had chorea due to HD (2 patients), tardive dystonia (1 patient) and hemiballismus (1 patient). Two patients with HD stopped treatment early (at 6th month); one because of worsening of symptoms and the second one because of lack of benefit. Therefore, these two patient observations were excluded from the study.

Olanzapine was well tolerated. We did not observe significant weight changes, orthostatic hypotension, somnolence or extrapyramidal side effects. One patient with OMD reported mild sedation at 8-month treatment; however, when olanzapine was titrated at a slower rate, sedation was not a problem any longer. The improvement of general clinical observation degree of patients is shown in Figure1.

Discusion

This study demonstrated that patients with various hyperkinetic movement disorders improved when treated with olanzapine and the best response was recorded in patients with chorea.

The atypical antipsychotic drug, olanzapine, has been found to be an effective treatment for hyperkinetic movement disorders. Olanzapine has a pharmacological profile that sets it apart from other neuroleptics. It binds to multiple receptor types with relatively low affinity for D2 receptor, which decreases the extrapyramidal side effects (18). In addition, olanzapine antagonizes a large number of receptors: Dopaminergic (D1, D2, D4), serotonergic (5HT2A, 5HT2C), muscarinic, H1 histaminic and alpha-adrenergic (3). The mechanism by which olanzapine may have beneficial effects is yet unclear. Preferential loss of D2 projection neurons, which are involved in a feedback loop normally active in the suppression of involuntary movements, is thought to be the pathophysiologic basis of chorea in HD (19). The D2 antagonist properties of olanzapine may explain some of its benefits. However, the effects at other receptors such as D4 may also be important, as D4 receptor density has been shown to be raised in HD, therefore the D4/D2 ratio of activity may be important (20) The beneficial effects of olanzapine on dystonia remains unclear, but it may be related to its antagonistic effect on the striatal–pallidal–thalamic–cortical pathway described by Delong et al. 1985 (21). Pharmacological studies suggested that dystonia emerges as an increased activity along both the ''direct'' and ''indirect'' pathways, attributed to the coexisting supersensitivity of both striatal D1 and D2 receptors (15). Thus, the antidystonic effect of olanzapine could be mediated via its antagonistic effect at these receptors. Moreover, the effect at other receptors such as D4 may also be important. Our study clearly indicates that olanzapine may be used for patients with various hyperkinetic movement disorders, especially chorea. In those patients, we saw an improvement of the general clinical observation degree after using longduration (24 months) olanzapine. To our knowledge, there were not a large number of long-term (≥2 years) studies on clinical effects of olanzapine (22,23).

Antipsychotic drugs are associated with a wide range of neurological complications , including extrapyramidal syndromes, neuroleptic malignant syndrome, serotonin toxicity, discontinuation symptoms and seizures. Recently, concern has focused on an increased risk of cerebrovascular events and death when antipsychotics are administered to elderly patients with dementia (24). When compared with anti-psychotic-free controls, elderly patients taking antipsychotics in monotherapy were at higher risk for first-ever stroke (25). Among the users of anti-psychotics, the unadjusted and adjusted stroke risk of patients treated with phenotiazines exceeded that found in subjects exposed to atypical antipsychotics (25). A meta-analysis of placebo-controlled trials of atypical antipsychotic drugs (aripiprazole, olanzapine, quetiapine, risperidone) in patients with dementia confirmed a

significantly increased risk for cerebrovascular events associated with atypical drug use and a small but significant increase in overall mortality (3.5% with drug vs. 2.3% with placebo) (24). Three cohort studies have compared the risk of death or stroke in elderly patients (>65 years) treated with conventional antipsychotics versus atypical antipsychotics (24). Two studies found no significant difference in risk of stroke between the two groups, while the third found that conventional antipsychotics were associated with a significantly higher adjusted risk of death (24). These studies suggest that conventional drugs should not automatically be used to replace atypical agents in elderly patients with dementia in response to safety concerns (24).

Extrapyramidal syndromes include acute dystonia, parkinsonism, akathisia, tardive dyskinesia and tardive dystonia. Extrapyramidal symptoms are less frequent with atypical than with conventional antipsychotics (24). A comprehensive meta-analysis studies lasting 1 year or longer showed that atypical drugs have an approximately fivefold lower risk of tardive dyskinesia than conventional antipsychotics during the first year of treatment (26).

We chose olanzapine because of its atypical pharmacological profile and less side effects. We did not observe serious adverse effects after long-term olanzapine treatment in this study.

This is a long-term study on the clinical effects of olanzapine in patients with various hyperkinetic movement disorders. The major limitations of this study were its open-label design, small number of patients, overweighting with HD patients, lack of a control group and heterogeneous patient group. We should state that the number of patients cannot be considered large enough for definitive conclusions. It is very difficult to perform a long-term placebo controlled study in heterogeneous patient group with various hyperkinetic movement disorders. Further double-blind, randomized controlled trials are needed to demonstrate conclusively the efficacy of olanzapine in hyperkinetic movement disorders.

Abbreviations

HD: Huntington's disease; OMD: oromandibular dystonia.

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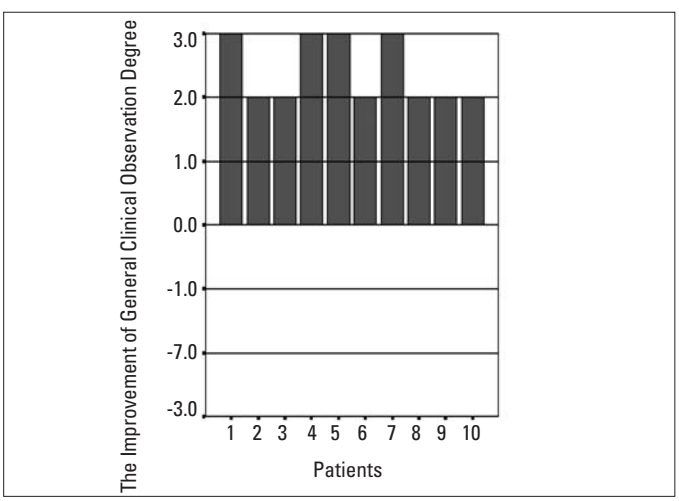

Figure 1: The Improvement of General Clinical Observation Degree in patients treated with olanzapine after 24 months

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