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The Effect of Clozapine on Tremor in Patients with Parkinson's Disease who were Initiated Clozapine For Psychotic Symptoms

Psikotik Semptomları Sebebi ile Klozapin Başlanmış Olan Parkinson Hastalarında Klozapinin Tremor Üzerine Etkisi

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Abstract

Aim: Tremor is one of the initial symptoms of Parkinson's disease and most of the patients suffer from it along the course of the disease. Levodopa and dopamine agonists are used as first-line therapy. Studies showed that clozapine can be effective on patients who are resistant or insufficiently responsive to these therapies. In this retrospective study, we searched the effect of clozapine on tremor.

Methods: We retrospectively analyzed the medical records of patients who have been followed in our Movement Disorders Clinic between the years 2005 and 2012. Fourteen patients using clozapine due to psychotic symptoms were included in the study. The patients were assessed using the Unified Parkinson's disease rating scale (UPDRS) at the beginning and after 2 months of constant dose of clozapine usage. Two patients were excluded from the study because of non-compliance with the treatment due to excessive sedation. Assessments were done on 12 patients.

Results: When the UPDRS scores before and after clozapine treatment examined, a statistically significant decrease was found in UPDRS-total, UPDRS-tremor, UPDRS-motor, and UPDRS-activities of daily living tremor scales after treatment.

Conclusion: Since clozapine may have a positive effect on tremor in Parkinson's disease, it can be considered as a treatment option for treatment-resistant psychotic symptoms. *(The Medical Bulletin of Haseki 2013; 51: 173-7)*

Key words: Parkinson's Disease, clozapine, tremor

Özet

Amaç: Parkinson hastalığında tremor hastalığın başlangıç belirtilerinden olup hastalık seyri boyunca hastaların büyük bir kısmında görülür. Levodopa, dopamin agonistleri ilk seçenek tedavi olarak kullanılmaktadır. Bu tedavilere yanıt alınamayan veya yetersiz yanıt alınan olgularda klozapinin etkili olabileceği çalışmalarda gösterilmiştir. Biz de bu retrospektif çalışmada klozapinin tremor üzerine etkilerini araştırdık.

Yöntemler: Bu çalışma 2005-2012 yılları arasında Hareket Bozuklukları Polikliniğinden takipli olan hastaların dosyaları incelenerek yapılmıştır. Çalışmaya psikotik semptomlar nedeni ile klozapin başlanmış olan 14 parkinson hastası alındı. Klozapin başlandığındaki Bileşik Parkinson Hastalığı Değerlendirme Ölçeği (BPHDÖ) skalaları ve 2 aylık sabit dozda klozapin kullanımı sonrası BPHDÖ skalaları incelendi. İki hastanın aşırı sedasyon nedeni ile tedaviyi düzensiz kullandıkları saptandığından bu hastalar çalışma dışı bırakıldı. Değerlendirmeler 12 hasta üzerinden yapıldı. Klozapinin tremor üzerine etkisi araştırıldı.

Bulgular: Tedavi öncesi ve tedavi sonrası BPHDÖ skorları incelendiğinde klozapin tedavisi ile BPHDÖ-total, BPHDÖ-tremor, BPHDÖ-motor, BPHDÖ-günlük yaşam tremor skalalarında istatistiksel anlamlı düşme olduğu gözlendi.

Sonuç: Parkinson hastalığında klozapin tremor üzerine olumlu etki gösterebileceğinden diğer medikal tedavilere dirençli psikotik semptomların görüldüğü Parkinson Hastalarında tedavi seçeneği olarak düşünülebilinir. *(Haseki Tıp Bülteni 2013; 51: 173-7)*

Anahtar Sözcükler: Parkinson Hastalığı, klozapin, tremor

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Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease presenting with motor findings such as tremor, bradykinesia, rigidity and non-motor findings. Resting tremor with a frequency of 4-7 Hz occurs in 75-80%of patients and is often the first symptom. Levodopa is the most effective treatment for treating the motor symptoms in Parkinson's disease. Dopa agonists such as pramipexole, ropinirole, pergolide, bromocriptine, and lisuride are effective on tremor in PD (1-5). Anticholinergic drugs have also been used for tremor in Parkinson's, however, presence of many side effects like sedation, confusion and hypotension, limit their use (5,6).

Psychosis in PD is characterized by hallucinations (primarily visual), delusions and other sensory disturbances such as illusions and 'sense of presence' hallucinations. Psychotic symptoms occur in 20-40%of PD patients (7,8). While the effects of clozapine on the psychotic symptoms of PD have been known, it was also shown to have effects on tremor (9-13).

In this study, we retrospectively compared the effect of clozapine on tremor reviewing the Unified Parkinson's disease rating scale (UPDRS) scale scores after 2 months of follow-up in 12 patients whose current PD treatment were not changed and who received clozapine regularly at a constant dose.

Methods

This study was carried out by investigating files of 14 patients who have been followed by the Movement Disorders Clinic in Haseki Training and Research Hospital between the years 2005 and 2012. The patients had been taking clozapine because of psychosis due to general medical condition according to DSM-4 criteria. Psychotic symptoms were formal visual hallucinations in particular. For each patient, we defined age, sex and disease duration at the time their hallucinations were suppressed by clozapine. UPDRS scores of the patients at the beginning and after 2 months of constant dose of clozapine usage were examined. Patients who had been receiving anticholinergic treatment and whose other medical treatment for PD had been changed were excluded from the study.

Two patients were excluded from the study at the end of two months because of non-compliance with the treatment due to excessive sedation. Assessments were carried out on 12 patients.

Indication for clozapine and maximum clozapine doses in patients were recorded. Patients who stopped taking the medication and their reasons to discontinue the treatment were determined. Leukocyte levels were recorded from weekly hemograms performed before and during the administration of clozapine.

Statistical Analyses

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programs were used for statistical analyses. Along with the descriptive statistical methods (Average, Standard deviation, frequency, proportion), the Wilcoxon signed-rank test was also used to compare the quantitative data while assessing the study data. A p value of less than 0.05 was considered statistically significant.

Results

The average age of the patients was 66.33±10.75 years (range: 47-79). 58.3%of subjects (n=7) were women and 41.9% (n=5) were men (Table 1).

The disease duration varied between 1 and 22 years with an average of 5.08±5.81 years. Clozapine dose varied between 6.25-75 mg/day with an average of 27.60±20.02 mg/day (Table 1).

None of the patients experienced agranulacytosis and no patient complained of weight gain during the follow-ups.

Table 1. Distribution of descriptive characteristics

		Min-Max	Mean Value±SD
Age		47-79	66.33±10.75
Onset of illness (age)		45-74	61.25±10.37
Disease duration (age)		1-22	5.08±5.81
Clozapine dose (mg/day)		6.25-75	27.60±20.02
		n	**(%)**
Gender	**Female**	7	58.3
	Male	5	41.7
H&Y scale	**Stage 1**	6	50
	Stage 2	6	50

Of the Parkinson Disease Assessment Scale Scores;

An average of 4.42±5.19 unit decrease was seen in post-treatment UPDRS total score compared to pre-treatment score which was found to be statistically significant (p<0.05). An average of 2.83±2.98 unit decrease was seen in post-treatment UPDRS motor score compared to pre-treatment score which was found to be statistically significant (p<0.05). An average of 2.00±1.32 unit decrease was seen in post-treatment UPDRS tremor scores compared to pre-treatment scores which was found to be statistically significant (p<0.05). The post-treatment versus pre-treatment change in UPDRS activities of daily living scores was not significant (p>0.05) (Table 2).

When the activities of daily living - tremor scale scores of patients were analyzed, it was seen that 4 patients had mild, 7 patients had moderate and 1 patient had severe tremor before the treatment. After the treatment, it was observed that tremor disappeared in two of the 4 patients with mild tremor and remained the same in 2 patients. It was seen that tremor disappeared in 2 of the 7 patients with moderate tremor, remained the same in 2 patients and changed to mild tremor in 3 patients. It was observed that severe tremor in 1 patient changed to mild tremor after the treatment.

A statistically significant decrease was found in activities of daily living-tremor score after treatment compared to before treatment (p<0.05) (Table 3).

Discussion

PD is a neurodegenerative disease presenting with motor findings, such as resting tremor, bradykinesia, rigidity and non-motor findings. Resting tremor is generally the first symptom. Levodopa, dopamin agonists and anticholinergic drugs are used as first-line therapies in the treatment (1-6,14). There are publications showing that clozapine is effective on cases unresponsive to first-line therapies (9-13).

Clozapine is an atypical antipsychotic drug acting via D4 receptor blockade. It has no negative effects on motor findings of PD due to the fact that it does not block D2 receptor unlike many other antipsychotic drugs. Clozapine treatment is among the first-line therapies in case of psychosis development related to general medical condition in PD (13). Its positive effects on dyskinesia and tremor were shown in some studies (9-13,16). Its mechanism of action is not clearly known.

Table 2. Results of Unified Parkinson's disease rating scales (UPDRS)

UPDRS	Pre-treatment		Post-treatment		
	Min-Max	Mean Value ±SD	Min-Max	Mean Value ±SD	p
UPDRS Total	10-56	32.00±15.67	10-52	27.58±13.22	0.005**
UPDRS Motor	5-38	21.58±10.34	5-37	18.75±9.47	0.005**
UPDRS Tremor	1-12	5.75±3.62	0-8	3.75±2.30	0.004**
UPDRS Activities of daily living	1-15	8.25±5.32	2-13	7.75±4.18	0.343

Wilcoxon Signed-Rank test **p<0.05

Table 3. Pre-treatment and post-treatment daily living activities-tremor assessments

Activities of daily living -Tremor	Pre-treatment	Post-treatment	
	n (%)	**n (%)**	
None	-	4 (33.3%)	
Mild	4 (33.3%)	6 (50.0%)	
Moderate	7 (58.3%)	2 (16.7%)	
Severe	1(8.3%)	-	**P :0.009****

Wilcoxon Signed-Rank test **p<0.05

In a study performed in 1986 (9), the efficacy of clozapine was investigated in 25 patients with tremor and it was observed to be effective in essential tremor and tremor of PD. In 1990, Friedman et al. (10) noted significant improvement in tremor in two of five patients with PD who had been taking clozapine for psychosis. Later, in a double blind study on 22 Parkinson's patients refractory to levodopa, the authors compared clozapine to benztropine for the treatment of tremor in PD and they found clozapine to be as effective as benztropine (11).

In a double blind study performed on 17 patients with PD (12), the effects of clozapine on Parkinson's mixed tremor (resting + postural) during acute and chronic use were investigated and positive effects on both resting and postural tremor were seen in 15 patients during acute administration and long-term use.

In our study, 2 of 14 patients were excluded from the study due to non-compliance with the treatment. Among the 12 patients assessed in the study, significant improvement was observed in tremor and the motor score of UPDRS of 10 patients and in tremor and activities of daily living scores of UPDRS of 8 patients. Although a statistically significant decrease was observed in post treatment UPDRS - total, UPDRS - motor, UPDRS - tremor scores, there was no difference in post-treatment activities of daily living scores of UPDRS compared to pre-treatment scores. We think that the lack of reflection of improvement in activities of daily living tremor sub-score on activities of daily living was caused by the fact that bradykinesia scores increased in a patient and this increase affected the UPDRS-activities of daily living statistics assessed at the end of two months.

In a study performed in 2010 on 61 patients (13), the effects of clozapine on psychosis and tremor were assessed and clozapine was initiated in 39 patients for psychotic symptoms, in 19 patients for tremor and in 6 patients for both tremor and psychotic symptoms. Positive effects of clozapine were observed in 50 patients. Improvement in tremor was observed in 20 of 25 patients after the treatment. Throughout the study, 11 patients passed away for other reasons while taking clozapine, 26 patients discontinued treatment due to worsening of motor symptoms, agranulocytosis, hallucinations, weight gain, myoclonus, elevation of blood glucose and decrease in leukocyte levels. In this study, clozapine doses of patients varied between 6.25 to 300 mg and average observation period was 39.9 months.

Clozapine was administered in 12.5-225 mg/day doses (69.6 mg/day) in a study investigating the effect of clozapine on dyskinesia and psychosis on 43 patients (16). Positive effects of clozapine were detected, however, side effects were observed in 26 patients at the time of clozapine initiation and 20 patients discontinued clozapine use for reasons such as death (5), leukopenia(3), thrombocytopenia (1), constipation (1), hallucination (1), and agitation (1). In this study, the total disease duration was 10.9±4.4 years and the average clozapine observation period was 3.5 years .

In our study, the follow-up duration of patients on constant dose of clozapine was 2 months. The clozapine dose varied between 6.25 and 75 mg/day with an average dose of 27.60±20.02 mg/day. Fewer side effects seen in our study might be due to the lower average age of patients, lower doses of clozapine and shorter follow-up duration.

Conclusion

It is concluded that tremor and psychotic symptoms might cause functional losses by affecting activities of daily living in patients with PD. With careful laboratory follow-up, clozapine treatment may be considered as a treatment option for treatment-resistant psychotic symptoms and tremor in patients unresponsive to other therapies.

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