COULD APOMORPHINE BE AN EFFECTIVE TREATMENT OPTION FOR REFRACTORY TREMOR IN PARKINSON'S DISEASE? A PILOT STUDY

Nilgün Çınar, Şevki Şahin, Sibel Karşıdağ
Maltepe Üniversitesi, Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul

ABSTRACT

Objective: *We aimed to evaluate the extent of the clinical efficacy of intermittent subcutaneous apomorphine in addition to oral treatment in patients with Idiopathic Parkinson's Disease experiencing serious, refractory tremor despite the use of optimal oral dopaminergic medication.*

Treatment response was assessed with the motor section of the Unified Parkinson's Disease rating scale (UPDRS). Tremor, rigidity and bradykinesia were scored by using specific items of the UPDRS.

Material and Method: *The study group included 13 consecutive patients with Parkinson's disease who have refractory tremor. Increasing doses of 1 mg, 2 mg, 4 mg subcutaneous apomorphine were used; peak improvement dose and UPDRS scores were determined after 30 minutes. The patients have used oral dopaminergic treatment plus subcutaneous apomorhine and they have been followed on weekly phone calls. The completion of the study was defined as the end of the 1st month. Finally, the UPDRS motor scores of the patients were compared to the basal scores.*

Results: *Three patients dropped out due to side effects. The average reduction rate of total UPDRS, tremor, bradykinesia and rigidity scores were found as 20.6%, 38.5%, 30.1% and 16.6% respectively. At the end of the first month, tremor, bradykinesia and rigidity scores were statistically improved in comparison to those of the baseline.*

Conclusion: *Subcutaneous apomorphine combined to oral dopaminergic medications may provide effective relief in serious and refractory rest tremor as well as bradykinesia and rigidity in selected Parkinson patients.*

Key Words: *Parkinson's disease, subcutaneous apomorphine, refractory tremor* ***Nobel Med 2013; 9(2): 100-103***

APOMORFİN PARKİNSON HASTALIĞINDAKİ DİRENÇLİ TREMOR İÇİN ETKİLİ BİR TEDAVİ SEÇENEĞİ OLABİLİR Mİ? PİLOT ÇALIŞMA

ÖZET

Amaç: Optimal oral dopaminerjik tedavi kullanımına rağmen ciddi, tedaviye dirençli tremoru olan idiyopatik Parkinson hastalarında, oral tedaviye ek olarak aralıklı subkutan apomorfin kullanımının klinik etkinliğinin değerlendirilmesi amaçlandı. Tedavi yanıtı birleşik Parkinson hastalığı değerlendirme ölçeği (BPHDÖ) motor bölümü ile değerlendirildi. Tremor, rijidite ve bradikinezi BPHDÖ'nin ilgili maddeleri kullanılarak puanlandı.

Materyal ve Metod: Çalışma grubu ardışık refrakter tremoru olan 13 Parkinson hastasını içermekteydi. Artan dozlarda 1 mg, 2 mg ve 4 mg subkutan apomorfin uygulandı. BPHDÖ puanları ve apomorfin tepe dozu 30 dakika sonra değerlendirildi. Hastalar oral dopaminerjik tedaviye ek olarak subkutan apomorfin kullandı ve hastalar haftalık telefon görüşmeleri ile takip edildi. Çalışmanın sonlanım noktası 1. ayın sonu olarak belirlendi. Sonunda, hastaların BPHDÖ motor puanları ilk puanları ile karşılaştırıldı.

Bulgular: Üç hasta yan etkiler nedeni ile çalışmadan ayrıldı. Toplam BPHDÖ, tremor, bradikinezi ve rijidite puanlarının ortalama düşüş oranı ise sırasıyla %20,6, %38,5, %30,1 ve %16,6 olarak bulundu. Birinci ayın sonunda, tremor, bradikinezi ve rijidite puanları ilk puanlara göre istatistiksel olarak düzelmişti.

Sonuç: Oral dopaminerjik tedaviye ek olarak verilen subkutan apomorfin ciddi ve refrakter istirahat tremoru ile birlikte bradikinezi ve rijiditesi olan seçilmiş Parkinson hastalarında rahatlama sağlayabilmektedir.

Anahtar Kelimeler: Parkinson hastalığı, subkutan apomorfin, refrakter tremor **Nobel Med 2013; 9(2): 100-103**

INTRODUCTION

The effect of subcutaneous apomorphine (APO) is very high in the management of "off" episodes in advanced Parkinson's disease (PD).[1] Although "off"episodes are the most disabling motor complications, in some cases, tremor is the dominant disability factor.[2] In this patient group, dopaminergic drugs cannot provide sufficiently effective treatment for rest tremor [1-3]. Hellmann et al. indicated that subcutaneous apomorphine can be effective in the treatment of tremor in Parkinson's disease as compared to the other symptoms.[4] If the tremor is the cardinal symptom and resistant to dopaminergic treatment, the use of apomorphine may be an alternative option. There are no adequate studies about the use of apomorphine except "off"periods in Parkinson's disease.

We aimed to evaluate the extent of the clinical efficacy of intermittent subcutaneous APO in addition to oral treatment in idiopathic PD patients experiencing serious, refractory tremor despite of dopaminergic medication usage. The response of tremor was compared to that of bradykinesia and rigidity.

MATERIAL and METHOD

The study group included 13 consecutive patients (5 women and 8 men) with idiopathic PD and experiencing serious, refractory tremor as the predominant symptom, who had received an optimal oral anti-PD regimen (levodopa/carbidopa and ≥1 other anti-PD medication) for ≥1 year before enrollment. Patients who had unstable and clinically significant cardiovascular, hepatic, renal, metabolic, respiratory, gastrointestinal, endocrine or hematologic diseases were excluded.

All patients had received oral dopaminergic therapy as levodopa and dopamine agonists (pramipexole or ropinirole), however they complained of sustained rest tremor which did not sufficiently improve. All patients were at Hoehn and Yahr stage 2, and none had developed motor fluctuations by the time of study.

Patients started antiemetic therapy (domperidone 10 mg, 3 times daily) for one week to reduce the side effects of apomorphine. Patients were encouraged to continue domperidon for 4 weeks after APO initiation. Anti-Parkinson medication was withheld for 12 h before APO initiation. Apomorphine was administered subcutaneously in increasing doses of 1 mg, 2 mg, and 4 mg with one hour interval. The patients were evaluated after each apomorphine administration at 15 min intervals. Peak improvement was produced 30 minutes after injection. The Unified Parkinson's Disease Rating Scale (UPDRS), motor section (part III) was used for assessment of the clinical severity of the patients. It was defined the rest and action tremor as item 20 and 21, bradykinesia as item 23-26, and rigidity as item 22 for all limbs. In statistical evaluation, the score of the most affected limb was considered as previously described.[5]

Table 1: Baseline and follow-up (after the administration of apomorphine) UPDRS scores

UPDRS	Mean (SD)		At the end of 1st month
Motor scores	Baseline	APO (30 min)	APO (30 min)
Total	23.7 (3.9)	18.8 (3)	19 (3)
Bradykinesia	6.3 (1.8)	4.4 (0.8)	4.3 (0.9)
Rigidity	1.8 (0.3)	1.5 (0.5)	1.4 (0.7)
Tremor	7 (1.4)	4.3 (1.2)	4.2 (1.3)

UPDRS: Unified Parkinson's Disease Rating Scale

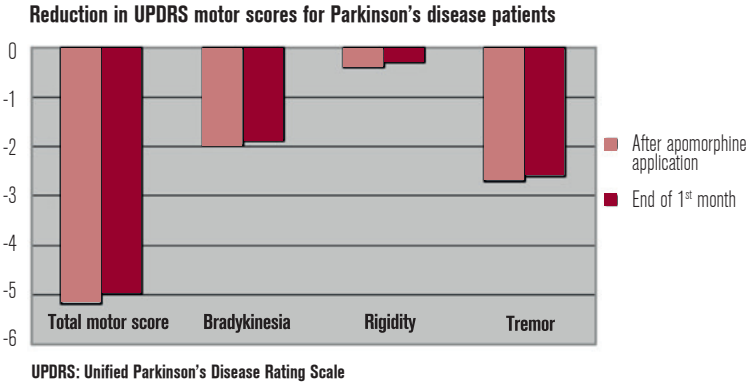

Figure 1: Reduction in baseline and follow-up (after the treatment of apomorphine) UPDRS scores. The mean reduction rate of UPDRS values are shown above the bars

The baselines scores of UPDRS after peak improvement dose was defined for APO. The patients were encouraged to take APO as needed concomitantly associated with oral dopaminergic medication. The endpoint of study was planned as the end of 1st month. Patients were asked to write daily apomorphine doses. The average daily doses were calculated for each patients. Responses to the treatment, side effects and drop-out interrogated by the same physician with the weekly phone call. At the end of the first month, the UPDRS was assessed for each patient and compared with the data. The study was approved by the local ethics committee. All the patients signed informed consent for use of APO.

Statistical Analysis

UPDRS scores were compared by Wilcoxon's test using SPSS 16 software. With respect to statistical significance, $p<0.05$ value was considered as significant. Demographic data were expressed as arithmetic mean±standard deviation (SD).

RESULTS

The mean age was 68.7±5.6 years, woman to man ratio →

was 5/8, and mean disease duration was 9±3 years (2-15). The mean dose of L-Dopa was 440±94 mg (range 250-550 mg), the mean doses of pramipexole and ropinirole were 2.7±1 mg (range 1-4.5 mg) and 11±1.7 mg (range 9-12 mg) respectively. The average daily dose of apomorphine was 9.3±3 mg (range 4-16 mg/day). The mean of UPDRS motor scores was 23.7±4 (15-29). Table 1 shows baseline and follow up clinical characteristics of the patients.

Thirty minutes following apomorphine use, the average total UPDRS score for the group decreased from 23.7±3.9 at baseline to 18.8±3 with a reduction of 20.6%. The tremor score dropped in all patients from 7±1.4 at baseline to 4.3±1.2 points after treatment with a reduction of 38.5%. The mean bradykinesia score decreased from 6.3±1.8 to 4.4±0.8 with a reduction of 30.1%. The mean rigidity score decreased from 1.8±0.3 to 1.5±0.5 with a reduction of 16.6% (Figure 1).

After subcutaneous apomorphine administration, UPDRS subscores for tremor, bradykinesia and rigidity all improved statistically compared to the initial scores (p=0.001, 0.007, 0.04, respectively). Three of patients could not use apomorphine, because of the side effects included nausea, orthostatic hypotension and displeasure about injection. Ten patients have continued APO plus oral dopaminergic treatment for one month. At the final assessment, the improvement in UPDRS motor scores has been better than basal scores of the tremor, bradykinesia and rigidity (p=0.004, 0.01, 0.05 respectively).

DISCUSSION

PD affects approximately 1-3% of people, older than age 65 years.[6] Tremor, bradykinesia and rigidity arise primarily from dopamine deficiency in the substantia nigra.[7] Current treatment of PD is symptomatic and is based on restoration of dopamine deficiency.[8] However, the response to the treatment of tremor, rigidity and bradykinesia are not the same. The drugs such as levodopa, carbidopa, benserazide, selegiline, amantadine, entacapone and tolcapone are effective on pre-synaptic region. The effects of bromocriptine, cabergoline, pramipexole, pergolide, ropinirole, rotigotine, and lisuride are effective in post-synaptic region.[1] Apomorphine is a potent dopaminergic agent that exerts its effect by direct stimulation of presynaptic and post-synaptic dopamine D1 and D2 receptors in subthalamic nucleus and globus pallidus interna.[9]

L-Dopa has a relatively short half-life. The combination with carbidopa causes it to extend to 1.5 hours.[10-13] The effect of subcutaneous apomorphine begins within 5-15 min, its half-life is about 40 minutes, ranging from 30 to 60 minutes, and the duration of effect is 40 to 90 min.[1,14-16] The therapeutic rescue dose ranged from 2 to 6 mg. During the clinical development program for subcutaneously injected apomorphine, patients require a mean of 3 rescue doses per day.[15] Apomorphine can be used as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes.[17] Intermittent subcutaneous apomorphine has recently approved for acute treatment of "off" episodes and has been shown in controlled clinical trials to be safe and highly effective in this indication.[18-20]

In some patients, rest tremor is serious, dominant symptom and refractory to oral dopaminergic treatment. We selected Parkinson patients who have refractory tremor despite the oral dopaminergic treatment. After we determined the peak dose with the apomorphine test, we ordered intermittent apomorfin plus oral dopaminergic therapy concomitantly for one month. Three patients were drop out in our study. In previous studies were showed that 2-3% of the patients discontinued apomorphine due to nausea and vomiting, 11% of the patients discontinued apomorphine due to orthostatic hypotension and syncope. Also, 26% of patients complained of injection site reactions.[4] This findings are concomitant with our results.

In the present series, we determined an average of 38.5% reduction in tremor with a 30.1% reduction in bradykinesia, and 16.6% reduction in rigidity in response with the addition of apomorphine to oral dopaminergic treatment. The improvement observed in tremor was higher than that observed in rigidity and bradykinesia. It may be an advantage in selected PD patients group.

Pogarell and Schrag also suggested that agonists such as pramipexole and ropinirole might have a special impact on tremor.[21,22] However, in patients with resistant tremor, dopamine agonists may be unsufficient despite high doses. In such patients, use of intermittent apomorphine may be considered as a treatment option. If intermittent subutaneous apomorphine is frequently applicated, continuous apomorphine infusion can be considered as an alternative treatment to the resistant tremor patients.

CORRESPONDING AUTHOR: Nilgün Çınar Maltepe Üniversitesi, Tıp Fakültesi, Nöroloji AD, Istanbul cinarnilgun@gmail.com

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